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CONTENTS

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PHAEOCHROMOCYTOMA, DIABETES, AND GLYCOSURIA[1]

By P. FREEDMAN, R. MOULTON, M. L. ROSENHEIM, A. G. SPENCER, and D. A. WILLOUGHBY

(From the Medical Unit, University College Hospital Medical School, London)

With Plate 32

The detection of phaeochromocytoma in patients with hypertension has excited increasing interest in recent years, chiefly because they form a small group in which the aetiology and mechanism of the hypertension are known, and in which removal of the tumour may effect a permanent cure. The fact that a phaeochromocytoma may also be the cause of diabetes, and may present itself as such, has attracted far less attention, although a number of well-documented cases have been reported (Duncan, Semans, and Howard, 1944; Goldner, 1947; de Vries, Rachmilewitz, and Schumert, 1949). It is our purpose in this paper to draw attention to the association of glycosuria with phaeochromocytoma, and we describe three patients who were diagnosed as having diabetes mellitus before the adrenal tumour was discovered, and a fourth who had glycosuria when first seen. An account is also given of the systematic search subsequently made for similar cases among the patients attending the diabetic clinic at University College Hospital.

Phaeochromocytomas are rare, but, as the syndrome has become more widely known, the diagnosis has become more frequent. Symington and Goodall (1953) collected 283 cases from reports published up to 1952, but many others have since been described. Minno, Bennett, and Kvale (1954) reported an incidence of approximately one in 1,000 in 15,984 consecutive post-mortem examinations at the Mayo Clinic, but in only three of their 15 cases was the diagnosis suspected during life. Graham (1951) found an incidence of one in 200 among hypertensive patients selected for sympathectomy. Diabetes is common, with an overall incidence of about four in 1,000 of the general population (Joslin, 1952); but in the age groups in which phaeochromocytoma is most common the incidence of diabetes is considerably greater, being about 10 in 1,000. Graham (1951) found an incidence of frank diabetes among cases of phaeochromocytoma of 10 per cent.; in an additional 9 per cent. there was reduced glucose tolerance. This incidence greatly exceeds the figure derived from chance association. The incidence of phaeochromocytoma in diabetic patients is unknown, since no record has been found of a search having been made for these tumours in patients attending a diabetic clinic.

[1] Received July 26, 1957

Many pharmacological tests are available for the detection of phaeochromocytoma, but none of these can easily be applied to large numbers of out-patients, while all may give false negative or false positive results (Helps, Robinson, and Ross, 1955). Probably the most reliable single method of detection is the estimation of adrenaline and noradrenaline in the urine (von Euler and Ström, 1957). A short screening test (Moulton and Willoughby, 1955), based on measurement of the change in the cat's blood-pressure following the intravenous injection of untreated urine, has now been in use in this Unit for three years, and has proved satisfactory. At least four of the 22 patients in whom phaeochromocytomas were found or confirmed by this method have had persistent glycosuria, and two of these patients had diabetes requiring large doses of insulin. It therefore seemed possible that some of the patients attending the University College Hospital diabetic clinic might have phaeochromocytomas. Since there were too many patients for the whole clinic to be screened, 144 of the 1,110 were selected, on a clinical basis described on page 314, and the short screening test was used to estimate the pressor-amine content of the urine.

Proved Cases of Phaeochromocytoma with Diabetes or Glycosuria

Case 1. A company director, aged 37 years, was referred to one of us with a history of diabetes with a markedly labile hypertension. A specimen of urine was found to contain a gross excess of adrenaline, so that a diagnosis of phaeochromocytoma was made before the patient was actually seen. From the age of 10 years he had been exceedingly nervous, and, although at 19 years he was accepted in Grade I for the Army, he soon began to complain of attacks of abdominal pain, and after several admissions to hospital he was invalided at 24 years with nervous dyspepsia and a raised blood-pressure. He continued to have abdominal pain, and at the age of 32 experienced his first attack. Attacks gradually increased in frequency and severity, and he was diagnosed as suffering from neurocirculatory asthenia. Two years later he became jaundiced, and was found to have gall-stones. A cholecystectomy was performed, apparently without any difficulty during anaesthesia or subsequently. The indigestion and abdominal pain were not relieved by this operation. At 36 years he was accepted, with loading, for a life insurance. Shortly afterwards his attacks became worse, and were then ascribed to a small hiatus hernia, which was confirmed radiologically. Four months later he lost weight, and developed thirst, polyuria, and glycosuria. He was diagnosed at another hospital as having idiopathic diabetes mellitus, and treated with a 1,750-calorie diabetic diet and soluble insulin 30 units twice a day. His doctor then discovered that the patient's blood-pressure was very labile and, observing it to change from 210/120 to 160/90 in a minute, referred him for investigation.

When the patient was seen, the history of strange attacks was obtained. These had occurred for five years, sometimes as often as three times a day, but he occasionally went for months without any. The onset was sudden, usually spontaneous, but occasionally brought on by anxiety or a heavy meal, but not by exercise or any particular posture. During an attack he felt tense and unable to move, and experienced an extremely unpleasant sensation which he described without prompting as a 'feeling of impending death'. He noticed his heart beating rapidly and forcibly, his hands became stone cold, and onlookers remarked on his intense pallor. The attacks varied in intensity, lasted for about

20 seconds to a minute, and gradually subsided, leaving him limp and exhausted. Although he considered that all his life he had sweated excessively, sweating was not a feature of the attacks. Headaches were not a prominent feature, but he often felt nauseated and distended with wind. His father had had mild glycosuria, and died at 65 years from a coronary thrombosis. One of his five sisters is hypertensive.

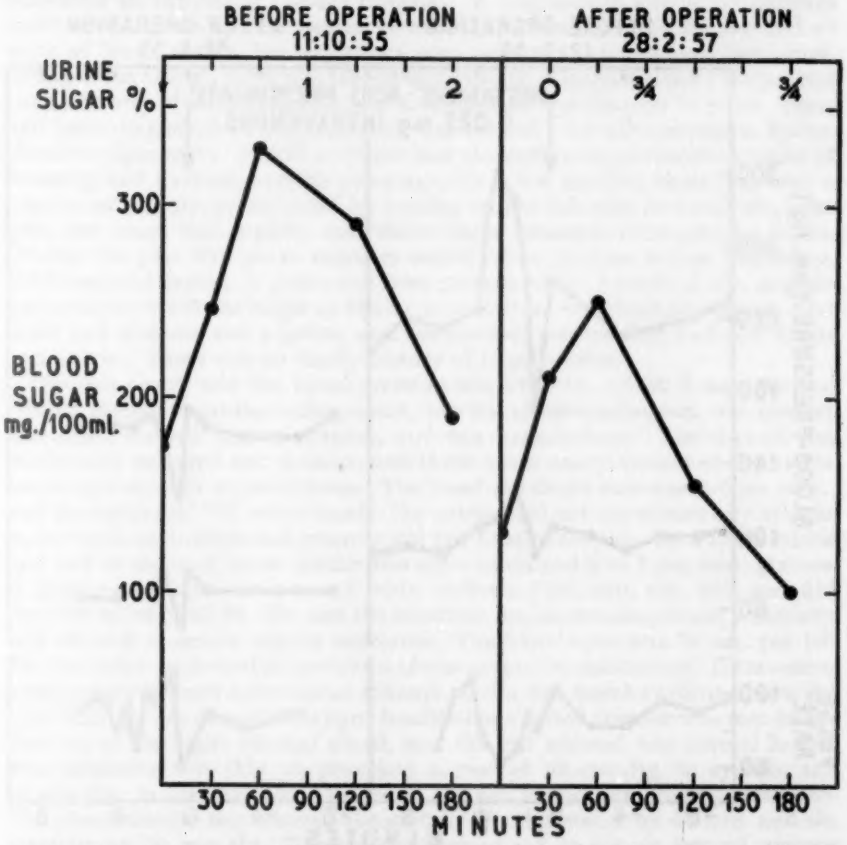

FIG. 1. Glucose-tolerance tests before and after removal of a phaeochromocytoma (Case 1).

In hospital the blood-pressure was constant at 190/100, and he had no spontaneous attacks. The heart sounds, chest radiograph, and electrocardiogram were normal. The fundi were normal. There was no abdominal mass, and an attack could not be precipitated by pressure on the loin. The urine contained no protein, and on microscopy was normal. The blood-urea was 24 mg. per 100 ml., and the clearance 173 per cent. The glucose-tolerance curve was frankly diabetic (Fig. 1). On a 1,750-calorie diabetic diet and soluble insulin, 32 and 24 units a day, the urine contained 0 to 0·5 per cent. glucose. The histamine test precipitated a severe attack, which was terminated with phentolamine. Intravenous pyelography showed two normal kidneys and a shadow in the right suprarenal area. On presacral oxygen insufflation a large right adrenal tumour was outlined, and the left adrenal was of normal size (Dr. C. J. Hodson) (Plate 32,

Fig. 4). The urine on several occasions contained a large excess of pressor amines (0·4 μg. per ml.), mostly adrenaline.

The tumour was removed without difficulty via a posterior approach by Mr. B. J. Harries. The operation was carried out under cortisone cover, and large quantities (total 250 mg.) of phentolamine were required to control the rise in blood-pressure. Noradrenaline was used for a short period to counter the

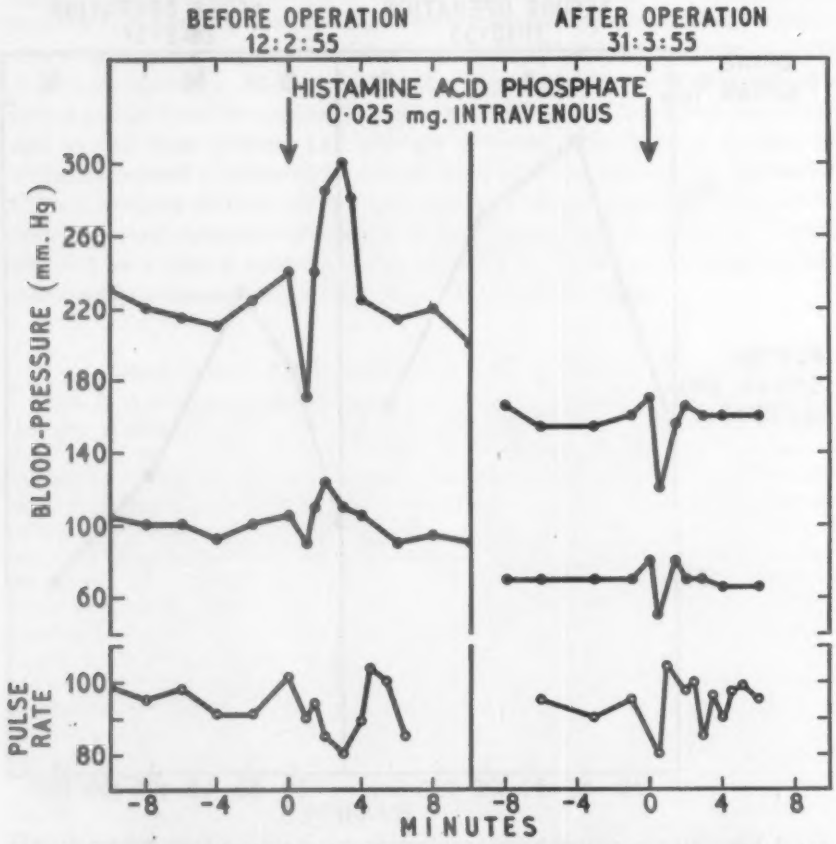

FIG. 2. Histamine tests before and after removal of a phaeochromocytoma (Case 2).

fall in blood-pressure on clamping the pedicle. Progress after operation was uneventful, and no insulin, cortisone, or noradrenaline was required. The blood-pressure fell to 110/70 by the third week, and 15 months later the casual blood-pressure with the patient ambulant was 135/75. The glucose-tolerance curve 15 months after operation is also shown in Fig. 1, and is still diabetic in type. The patient has been completely relieved of his symptoms, is free of attacks and abdominal pain, and has no glycosuria with only slight restriction of dietary carbohydrate. The pressor-amine content of the urine has been normal since removal of the tumour. The tumour weighed 150 g., and the histological appearance was characteristic of a benign phaeochromocytoma. It contained 12 mg. per g. of pressor amines, most of which was identified as adrenaline.

Case 2. A housewife aged 65 years was treated for diabetes by a diet and 'lente' insulin for more than a year. When she later developed hypertension the diagnosis of phaeochromocytoma was considered likely by Dr. M. Harington, and the urinary excretion of pressor amines was found to be grossly raised. There was a history, extending over five years, of thirst, polyuria, malaise, and loss of weight, and glycosuria was discovered about a year before her present admission to University College Hospital. A diagnosis of idiopathic diabetes mellitus was made, and on treatment with a 1,250-calorie diabetic diet and 40 units of 'lente' insulin her symptoms were relieved. At this time her blood-pressure was 150/90, but a year later it was 240/100. On close inquiry the patient gave a history of trembling attacks and headaches over the past 16 years. These had been diagnosed as Parkinsonism and treated with ethopropazine hydrochloride, ('lysivane'). For 11 years she had also suffered spontaneous attacks of sweating and flushing, and six years ago, for a few months, there had been a number of attacks, precipitated by turning on her left side, in which she went pale, her heart beat rapidly, and there was a sensation of impending death. During the past five years exertion would often produce severe headaches, giddiness, and pallor. A goitre had been present since 16 years of age, and she had noticed that it was larger on the days when there was much glycosuria. One sister had diabetes and a goitre, and her mother, one brother, and two sisters had goitres. There was no family history of hypertension.

She was obese, and the blood-pressure was 210/110. Chest X-rays demonstrated moderate cardiac enlargement, but the electrocardiogram was normal. The fundi showed narrow arteries, and one haemorrhage. The thyroid was moderately enlarged and nodular, and there was a coarse tremor of the hands, but no eye signs of thyrotoxicosis. The basal metabolic rate was +6 per cent., and the uptake of ^{131}I was normal. The patient did not experience any attacks in the ward, and abdominal pressure did not precipitate one. On a 1,250-calorie diet and 40 units of 'lente' insulin the urine contained 0 to 1 per cent. glucose. A glucose-tolerance curve was frankly diabetic (290, 430, 420, 390, and 310 mg./100 ml. at 0, 30, 60, 120, and 180 minutes), and an insulin-glucose sensitivity test showed complete insulin resistance. The blood-urea was 36 mg. per 100 ml.; the urine contained no protein, and was normal on microscopy. Intravenous pyelography showed two normal kidneys, and a soft-tissue swelling above the right kidney. On presacral oxygen insufflation a round tumour was seen in the position of the right adrenal gland, and the left adrenal was normal in size. The histamine test (Fig. 2) provoked a rise of 98 mm.Hg. in systolic and 30 mm.Hg. in diastolic blood-pressure, and the tremor was greatly increased. The phentolamine test lowered the systolic blood-pressure by 40 mm. and the diastolic by 30 mm.Hg. The urine contained 0·3 to 0·4 μg. per ml. pressor amines, mostly adrenaline.

The tumour was removed by Mr. B. J. Harries via a posterior approach. During the operation phentolamine (total 45 mg.) was used to control the rise in blood-pressure. After ligation of the adrenal vein there was a profound fall in blood-pressure, and an intravenous infusion of noradrenaline was required during the next 10 hours. The course after operation was otherwise uneventful. The tumour weighed 35g., and the histological appearance was that of a simple phaeochromocytoma. After the operation the patient had no further attacks, although some tremor persisted. There was no glycosuria, and the fasting blood-sugar was 109 mg. per 100 ml. The blood-pressure was steady at 140/90, and a further histamine test gave a normal result (Fig. 2). Three months after the operation, however, the blood-pressure was 200/100, there was glycosuria (0 to 0·5 per cent.), and a glucose-tolerance curve was mildly diabetic.

Some resistance was shown in the insulin-sensitivity test, but less than before the operation. For two years the patient has remained well, the blood-pressure showing only slight fluctuations. There have been traces of sugar in the urine on several occasions, but she has been taking a normal diet and no insulin. The pressor-amine content of the urine has been normal since removal of the tumour.

Case 3. A female clerk, aged 34 years, was a patient of Mr. R. Vaughan Hudson at the Middlesex Hospital. She was referred to Dr. J. D. N. Nabarro when she developed glycosuria after an operation for excision of glands in the neck.

For 12 years, since 1942, she had suffered from attacks of palpitations, 'thumping' in the head, weakness of the limbs, and headaches. These attacks were frequently precipitated by exercise. A diffuse goitre was noted at that time, and the basal metabolic rate was −1 per cent. She was then considered to be suffering from an anxiety state. During the next two years her symptoms persisted unchanged, and she was referred for a surgical opinion. The goitre was found to be nodular, and partial thyroidectomy was undertaken. A circumscribed tumour was found in each lobe, and on section was found to be an anaplastic carcinoma. The basal metabolic rate was +23 per cent., and a course of deep X-ray therapy was given, followed by total thyroidectomy. Microscopy of the excised gland again showed carcinomatous change. After operation attacks were observed in which the pulse-rate rose to 140 per minute and the blood-pressure to 240/150. After discharge from hospital, and for the next six years, the attacks were much less frequent. She then had a severe recurrence of the attacks, which coincided with a haemoptysis, which she felt came from her throat and not her chest. Chest X-rays showed no abnormality. Two years later another haemorrhage occurred, but the radiograph was again normal. The following year she had a further haemorrhage, and the attacks of palpitation increased in frequency. At this time she was myxoedematous, with a basal metabolic rate of −27 per cent. and very low ^{131}I uptake in the neck. She was referred for thoracic investigation. Bronchoscopy and bronchography revealed no abnormality. Treatment with thyroxine was commenced. A year later she was found to have secondary deposits in the glands of the neck. The glands were excised, and contained undifferentiated carcinoma. After operation she had a severe attack of sweating, with tachycardia, hypertension, and glycosuria (2 per cent.). The diagnosis of phaeochromocytoma was considered likely by Dr. J. D. N. Nabarro, and a specimen of urine was sent to this laboratory for pressor-amine assay. There was no family history of hypertension or endocrine disorder.

When the patient was admitted to the Middlesex Hospital in 1954 the resting blood-pressure was 115/75, the heart sounds and chest X-rays were normal, and an electrocardiogram showed low-voltage curves. There was no abdominal mass, and an attack was not precipitated by pressure on the loin. The urine contained no protein, and on microscopy was normal, but the sugar content varied from 0 to 2 per cent. The blood-urea was 20 mg. per 100 ml. The glucose-tolerance curve was frankly diabetic, a fasting blood-sugar of 176 mg. rising to a maximum of 276 mg. per 100 ml. The 24-hour ^{131}I uptake in the neck was less than 3 per cent., and the serum-cholesterol level was 300 mg. per 100 ml. The urine was found to contain a large excess of pressor amines (2 μg. per ml.), mostly noradrenaline. The histamine test provoked a severe hypertensive attack, which was terminated with phentolamine. An intravenous pyelogram showed two normal kidneys, with some outward displacement of both upper

calyces, more particularly on the left side. Presacral air insufflation showed a very large left adrenal and a slightly enlarged right adrenal gland.

The left adrenal gland, which contained a tumour weighing 115g., was removed via a posterior approach by Mr. Vaughan Hudson. Phentolamine was used to control the blood-pressure during manipulation of the tumour, and noradrenaline was required to maintain the blood-pressure after removal of the

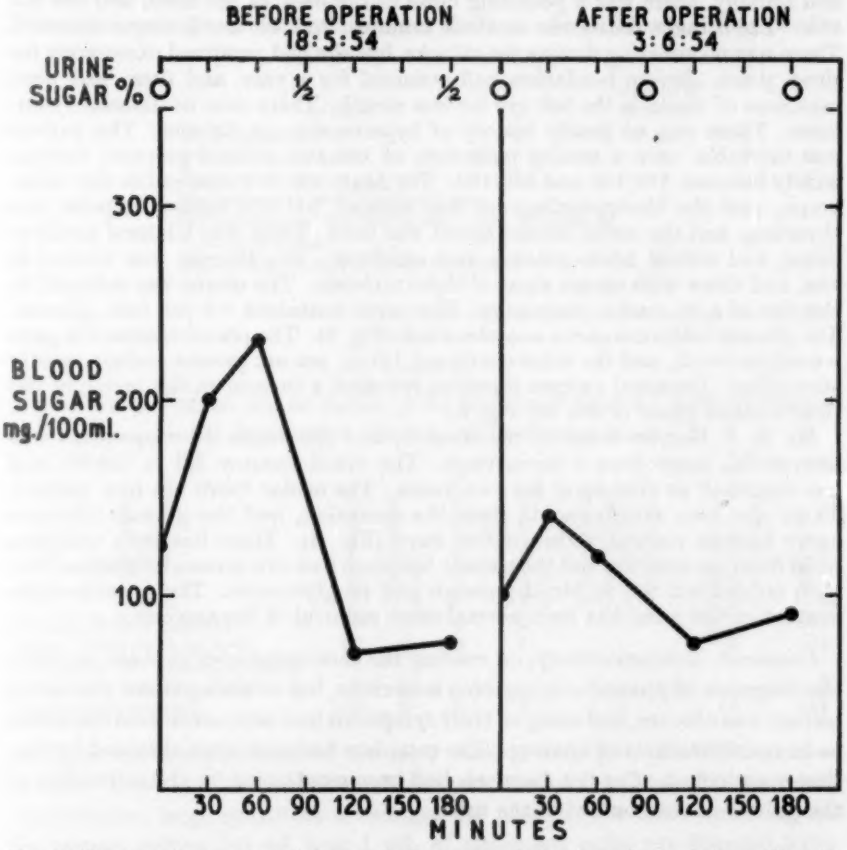

FIG. 3. Glucose-tolerance tests before and after removal of a phaeochromocytoma (Case 4).

tumour. The course after operation was stormy, and the blood-pressure continued to fall despite the use of large amounts of noradrenaline and cortisone. Her condition steadily deteriorated, and she lapsed into coma. In spite of vigorous prophylactic measures she developed pneumonia, and died four days after operation. Post-mortem examination showed bronchopneumonic changes in the lungs, and an enlarged right adrenal gland containing a metastasis of thyroid carcinoma. The tumour removed at operation, on section, contained dark brown haemorrhagic tissue, with areas of yellowish-white cardinoma invading it. Microscopy showed a phaeochromocytoma in the left adrenal gland.

Case 4. A housewife aged 32 years was referred from the Obstetric Unit when four months pregnant, because of malignant hypertension, peculiar attacks,

and glycosuria. This case has been reported in detail in another connexion (Helps, Robinson, and Ross, 1955).

The attacks had occurred two or three times daily for the past five years, and were brought on by exertion, laughing, or lying on the left side. In them she felt a horrible sensation in the epigastrium, her fingers and face went white, and observers had said she looked like a corpse. She felt her heart beating rapidly and forcibly, there was a pounding noise in the back of her head, and she felt sick. The attacks lasted two to three minutes, and left her feeling exhausted. There was no sweating during the attacks, but she had perspired excessively for three years. Severe headaches had occurred for a year, and there had been mistiness of vision in the left eye for one month. There were no diabetic symptoms. There was no family history of hypertension or diabetes. The patient was excitable, with a resting pulse-rate of 100 and a blood-pressure varying widely between 170/100 and 220/160. The heart was not enlarged in the radiograph, and the electrocardiogram was normal, but the cardiac impulse was thrusting, and the aortic second sound was loud. There was bilateral papilloedema, and retinal haemorrhages and exudates. The thyroid was normal in size, and there were no eye signs of thyrotoxicosis. The uterus was enlarged to the size of a 16 weeks' pregnancy. The urine contained 0·5 per cent. glucose. The glucose-tolerance curve was abnormal (Fig. 3). The phentolamine test gave a positive result, and the urine contained 1·5 μg. per ml. pressor amines, mostly adrenaline. Presacral oxygen injection revealed a tumour in the region of the right adrenal gland (Plate 32, Fig. 5).

Mr. B. J. Harries removed the tumour, and the course after operation was uneventful, apart from a miscarriage. The blood-pressure fell to 130/90, and has remained at that level for two years. The ocular fundi are now normal. There has been no glycosuria since the operation, and the glucose-tolerance curve became normal within a few days (Fig. 3). There has been complete relief from the attacks, and the patient has since had two successful pregnancies, with no marked rise in blood-pressure and no glycosuria. The pressor-amine content of the urine has been normal since removal of the tumour.

Comment. Retrospectively, on reading the case summaries of these patients, the diagnosis of phaeochromocytoma is obvious, but in each patient the initial history was obscure, and many of their symptoms had been considered elsewhere to be manifestations of anxiety. The complete histories were obtained by further questioning, after the diagnosis had been established by the estimation of the pressor-amine content of the urine.

Screening Diabetic Patients

Selection of patients and methods. Since it was not possible to screen all the patients attending the diabetic clinic, they were selected as in Table I, a diastolic pressure of 100 mm.Hg or more in out-patients being used as a criterion of hypertension, and patients with evidence of diabetic nephrosclerosis being excluded. In most cases it was possible to distinguish hypoglycaemic episodes from other attacks, and many of the patients investigated were not taking insulin. This investigation was made concurrently with a general study of hypertension and diabetes (Freedman, Moulton, and Spencer, 1958). Random samples of urine were collected in sterile bottles containing 50 mg. of ascorbic acid as a

preservative. Samples of 24-hour collections were tested whenever the random samples had shown a high content of pressor amine. Random samples were used because, although these may not always be so representative as a 24-hour collection, the latter often contains large amounts of histamine. Histamine

TABLE I

The Criteria used for Selecting the Diabetic Patients whose Urinary Pressor-Amine Excretion was Estimated

Criteria	*Number of patients*
Hypertension	119
Unexplained attacks	3
Thyrotoxicosis	2
Hypertension and thyrotoxicosis	3
Hypertension, thyrotoxicosis, and attacks or anxiety state	2
Hypertension and attacks or anxiety state	15
Total	144

(out of 1,110 patients attending the clinic)

TABLE II

The Urinary Pressor-Amine Levels of the Groups of Diabetic Patients Selected for Screening to Exclude Phaeochromocytoma

Pressor-amine excretion (as adrenaline)	*Hypertension*	*Unexplained attacks*	*Thyrotoxicosis*	*Hypertension and thyrotoxicosis*	*Hypertension, thyrotoxicosis, and attacks or anxiety state*	*Hypertension and attacks or anxiety state*	*Number of patients*
Normal (0–0·05 μg./ml.)	93	1	1	2	1	8	106
Raised (0·05–0·15 μg./ml.)	25	1	2	1	1	6	36
Indicative of phaeochromocytoma (over 0·15 μg./ml.)	1	..	..	..	..	1	2
Number of patients	119	2	3	3	2	15	144

confuses the interpretation of the test, since it may give pressor, depressor, or mixed responses, and, while small amounts can be antagonized in the cat by mepyramine, large quantities invalidate the test. In the short screening test for pressor amines 0·5 ml. and 1 ml. of untreated urine are injected intravenously into the anaesthetized cat, and the response of the blood-pressure on a continuous recording is compared with that produced by standard solutions of adrenaline and noradrenaline (Moulton and Willoughby, 1955).

Results. The results are summarized in Table II. Normal figures were obtained in 106 (73 per cent.) of the selected diabetic patients, while 36 (26 per cent.) were excreting abnormally large amounts of pressor amines in the urine, and in a further two the levels obtained were in the range usually found in cases of phaeochromocytoma. In essential hypertension, if there is an increased excretion of pressor amines in the urine, it is usually an excess of noradrenaline, but in these 36 diabetic patients, 33 of whom were hypertensive, the increase was mainly of adrenaline. One hundred and nineteen of the 144 diabetic patients

were selected for screening because of hypertension, and 26 (22 per cent.) of these patients had an abnormally high adrenaline excretion. Of the 25 other diabetic patients screened, many of whom suffered from anxiety states, 12 (48 per cent.) were excreting excessive amounts of adrenaline. There was no difference in the proportion of patients taking insulin in the two groups. In our patients the excretion of pressor amines in the urine was not related to sex or age. Burn (1953) has reported an increase in noradrenaline excretion with increasing age (three months to 63 years), but our patients were all in the same age group of 40 to 65 years. Of the hypertensive diabetic patients not taking insulin, only 15 per cent. had an increased excretion of pressor amines in the urine, whereas 40 per cent. of those who were taking insulin had high levels of adrenaline in the urine (0·05 to 0·15 μg. per ml.). This finding strongly suggests that insulin may have increased the production or excretion of adrenaline. Von Euler and Luft (1952) have reported an increased excretion of adrenaline after insulin hypoglycaemia, and it is possible that even a mild degree of hypoglycaemia may produce a release of adrenaline. We have no details of the blood-sugar levels in our patients at the time the random specimens of urine were taken.

The two diabetic patients with a persistently high excretion of adrenaline, strongly suggestive of phaeochromocytoma, are described below:

1. A man aged 61, a diabetic for 20 years, was known to have had hypertension for 10 years and complete heart-block for five years, and had recently recovered from congestive cardiac failure. There was no history of attacks, but he had always sweated profusely. A family history of hypertension was obtained, but none of diabetes. Five estimations of his urinary pressor amines gave values of about 0·3 μg. adrenaline per ml. Straight X-rays of the abdomen clearly showed the renal outlines, but no adrenal tumours could be seen. Since he was unfit for operation, it was not considered justifiable to subject him to a phentolamine test, or to X-ray studies after oxygen injection.

It is possible that complete heart-block may be associated with an increased production and excretion of pressor amines, but we have not found the pressor-amine excretion increased in chronic heart failure, although there is a temporary increase after myocardial infarction (Forssman, Hansson, and Jensen, 1952). The urinary pressor-amine excretion was within normal limits in one other case of complete heart block.

2. An obese woman aged 60, diabetic for 25 years, had advanced vascular disease, hemiplegia, mental deterioration, blindness, and incontinence; she had had a mid-thigh amputation for gangrene. Her basal blood-pressure was 150/90, blood-urea 40 mg. per 100 ml., and urine protein 1 part in 1,000, and there was a chronic urinary infection. She had frequent attacks of profuse sweating in which the blood-pressure rose to 220/140. The blood-sugar in these attacks was over 400 mg. per 100 ml., and at the time the patient was not receiving insulin. Between attacks the excretion of pressor amines was within the limits found in essential hypertension, but after an attack it was increased to over 0·4 μg. adrenaline per ml. The patient was too obese and too mentally confused for X-ray studies. A phentolamine test could not be done, because the hypertensive attacks were of short duration, and a histamine test was considered unjustifiable. The patient died two months later, and autopsy was refused.

It appears possible that these two patients, the only two in the series of diabetics investigated who had a markedly increased excretion of pressor amines, had phaeochromocytomas. Unfortunately their clinical condition prevented further investigation or surgical exploration.

Discussion

The history remains the most important factor in the clinical diagnosis of phaeochromocytoma. The patients with diabetes described in the first part of this paper were immediately suspected of having phaeochromocytomas when seen by doctors who had experience of this condition. Yet all of them had attended clinics elsewhere, or had been seen by a number of doctors, for periods of many months or years, and all had a variety of diagnoses attached to them. Most of the symptoms and signs produced by a phaeochromocytoma can be explained by the action of excessive amounts of circulating noradrenaline or adrenaline. Many tumours appear to secrete mainly one or the other of the pressor amines, but the clinical syndromes they produce are not entirely distinct. The majority of phaeochromocytomas cause hypertension of some degree, but those which mainly secrete adrenaline usually produce metabolic disturbances, diabetes, and anxiety, in addition to the hypertension (for example Cases 1 and 2). Noradrenaline-secreting tumours, however, mainly cause symptoms consequent on the rise in blood-pressure (for example, Case 4). Of 22 patients with phaeochromocytoma found or confirmed by the short screening test, the tumours were predominantly adrenaline-secreting in only two, and these two had frank diabetes. The family history is not given in the majority of the reported cases of phaeochromocytoma, and it might be assumed that a family history of diabetes would make the diagnosis of phaeochromocytoma very unlikely. This is not the case, however, since two of our four proven cases (Cases 1 and 2) of phaeochromocytoma associated with diabetes gave family histories of diabetes. Familial phaeochromocytoma is extremely rare, only five such families having been reported (see Kelsall and Ross, 1955).

While adrenal medullary tumours may occur at any age, we have found no record of their association with diabetes below 20 years of age. Since West, Shepherd, and Hunter (1951) have shown that the adrenal glands in childhood contain very little adrenaline as compared with noradrenaline, it seems that a child with diabetes but without hypertension is unlikely to have a phaeochromocytoma. The age of onset of symptoms in our four cases was 32, 49, 22, and 27 years respectively. Hypertension is rare in diabetic patients under the age of 40; the youngest hypertensive diabetic in the University College Hospital clinic was aged 44 years. This finding immediately suggests that every hypertensive diabetic, between 20 and 50 years of age, should be further investigated to prevent a phaeochromocytoma being missed.

Severe hypertension is rare in idiopathic diabetes mellitus, but common in diabetes associated with a phaeochromocytoma, and it has been found that advanced hypertensive retinopathy, as distinct from diabetic retinopathy, does

not often occur in idiopathic diabetes mellitus (Freedman, Moulton, and Spencer, 1958). Hypertensive retinopathy is common in phaeochromocytoma (for example, Case 4), and true diabetic retinopathy has never been reported in this condition. It follows that in any diabetic patient with severe hypertensive as distinct from diabetic retinopathy the pressor-amine content of the urine should be measured. The hypertension in diabetes due to a phaeochromocytoma may be paroxysmal or sustained, and the blood-pressure is frequently raised to some extent between attacks (for example, Cases 1 and 2). Similarly, the disturbance in carbohydrate metabolism may be accentuated in paroxysms, but usually, if it is severe enough for the patient to have diabetic symptoms, glycosuria and high blood-sugar levels are constantly present (for example, Cases 1 and 2). A high blood-sugar level during attacks, sometimes followed by glycosuria, is common in patients who have a phaeochromocytoma (Graham, 1951), and such patients may have a diminished glucose tolerance though they have not been regarded as diabetics (for example, Case 4). Removal of a phaeochromocytoma leads to very considerable improvement of diabetic symptoms, but the glucose-tolerance test may still show considerable intolerance of carbohydrate (Cases 1 and 2), or it may revert rapidly to normal (Case 4). Diabetic coma has not been reported in phaeochromocytoma, although coma due to a cerebro-vascular catastrophe is common. De Vries, Rachmilewitz, and Schumert (1949) have reported a case of phaeochromocytoma with severe ketosis and acidosis which responded to insulin, and Duncan, Semans, and Howard (1944) have described one with ketosis during a bout of pneumonia. Thus patients with a phaeochromocytoma may show none of the symptoms, signs, or biochemical characteristics of diabetes, or they may exhibit every grade of severity, including advanced diabetic ketosis. It is well recognized that patients with diabetes may present a variety of syndromes, such as chest pain from coronary artery disease, abdominal pain in association with acidosis, and coma from cerebro-vascular accident, ketosis, or hypoglycaemia. Similarly, patients with phaeochromocytomas may (rarely) present a variety of bizarre syndromes (Rabin, 1929; Gilliland and Daniel, 1951; Jelliffe, 1952), such as severe pain in the chest or abdomen associated with shock, or coma due to a cerebro-vascular catastrophe, and if the urine contains glucose the patient's condition may again be mistaken for diabetes.

Although the adrenal cortex is not directly involved in phaeochromocytoma, the tumour sometimes compresses and renders functionless the adrenal cortex on the same side. The opposite adrenal will then hypertrophy, and in at least one patient this enlarged gland has been mistaken for the tumour and removed, with fatal results (Volhard, 1931). In spite of the bizarre case of adrenal virilism which regressed after removal of a phaeochromocytoma (Neff, Tice, Walker, and Ockerblad, 1942), and a malignant phaeochromocytoma simulating adrenal carcinoma (McGavack, Benjamin, Speer, and Klotz, 1942), there is normally no difficulty in differentiating between Cushing's syndrome and phaeochromocytoma.

Patients with phaeochromocytomas have often had a wrong diagnosis of

diabetes and thyrotoxicosis attached to them, and this differentiation is numerically important, because the coexistence of diabetes and thyrotoxicosis is not uncommon. Root (1952) found hyperthyroidism in one per cent. of his diabetic patients, and there were 15 such cases in the University College Hospital diabetic clinic (1·4 per cent.). Such patients often have a labile hypertension (14 out of 15), anxiety, sweating, tremor, and tachycardia, in addition to their diabetes and high basal metabolic rate. They have, therefore, many of the clinical features which characterize an adrenal medullary tumour. Case 3 illustrates the association of phaeochromocytoma and thyroid carcinoma. Thyroidectomy has been performed in several cases of phaeochromocytoma (Beer, King, and Prinzmetal, 1937; Bartels and Cattell, 1950; Richards and Hatch, 1951) with no benefit and a very high mortality rate, and thiouracil derivatives have also been given, usually without effect. In phaeochromocytoma evidence of hypermetabolism is common, such as tachycardia, fever, sweating, and a raised basal metabolic rate. To add to the difficulty in diagnosis, the thyroid gland is sometimes enlarged. The ^{131}I uptake, however, was high in our 14 diabetics with thyrotoxicosis, and normal in the patients with phaechromocytomas in whom it has been recorded. None of our thyrotoxic diabetic patients had a markedly increased excretion of pressor amines, whereas this increase was great in the cases of phaeochromocytoma. It follows that diabetic patients with apparent thyrotoxicosis and a normal uptake of ^{131}I should have the excretion of pressor amines measured to exclude or confirm the diagnosis of phaeochomocytoma.

Symington and Goodall (1953) have reviewed the histological appearances of phaeochromocytomas, and there is no special histological type associated with diabetes. Hillarp and Hökfelt (1953–4) have shown that adrenaline and noradrenaline are secreted by different groups of cells in the adrenal medulla. A specific cell-type of phaeochromocytoma for those tumours which secrete mainly adrenaline or noradrenaline has not yet been demonstrated.

The mechanism by which a phaeochromocytoma may cause diabetes is uncertain. It is considered that the high plasma concentration of adrenaline, and to a much smaller extent of noradrenaline, causes a rise in blood-sugar by accelerating glycogenolysis in the liver. This may well increase the rate of secretion of insulin by the pancreas, and eventually produce a temporary or permanent exhaustion of the islets of Langerhans. Estimations of the plasma-insulin in patients with diabetes and phaeochromocytoma would provide direct evidence in relation to this hypothesis. It is also possible that adrenaline may antagonize insulin by its action on the anterior pituitary gland, causing an increased secretion of corticotrophin, and thus indirectly stimulating the secretion of hydrocortisone. Estimations of the plasma-hydrocortisone, and of the excretion of 17-ketogenic steroids, would test this hypothesis directly. Insulin-sensitivity tests in diabetes due to a phaeochromocytoma may show insulin resistance (Case 2), affording indirect evidence of an increase in insulin antagonists. The insulin requirements are usually greatly decreased within 24 hours of removal of the tumour, and the patients may be completely cured of their diabetes. That the pancreas is not necessarily permanently damaged is shown by the return to

normal of the glucose-tolerance curves after the removal of the phaeochromocytoma. Some impairment, however, of carbohydrate metabolism frequently remains for months or years (Cases 1 and 2). Just as the removal of a phaeochromocytoma does not always cure the hypertension, especially hypertension of long duration, it also does not invariably cure the diabetes (Joslin, Root, White, and Marble, 1952). In such patients there is always the possibility of multiple tumours as a cause of persistent symptoms, and, since in 10 per cent. of patients there is more than one tumour, we always estimate the urinary pressor amines at one week and again at three months after the operation. A second, rare cause of diabetes persisting after the removal of the tumour is the chance association of idiopathic diabetes and phaeochromocytoma.

We conclude that phaeochromocytoma should be considered in the diagnosis of any young hypertensive diabetic, and in hypertensive diabetic patients of any age if other suggestive features are present. The majority of patients suspected of a phaeochromocytoma are eventually shown not to have one, but if a search is not made for these tumours they will certainly not be found.

We are grateful to Dr. J. D. N. Nabarro and Dr. E. E. Pochin for permission to publish details of their patients; to Mr. B. J. Harries and Mr. Vaughan Hudson, who performed the operations; to Dr. C. J. Hodson for his X-ray studies; to Professor M. Maizels for the routine clinical pathological chemistry; and to Mr. V. K. Asta for the charts.

Summary

1. Four patients, two with severe diabetes and two with persistent glycosuria due to a phaeochromocytoma, are described.

2. A systematic search, including measurement of the excretion of pressor amines in the urine, for similar cases, was made among 1,110 diabetic patients, and two further possible cases were found.

3. The clinical and biochemical features which were important in the diagnosis are discussed.

4. The association between phaeochromocytoma and diabetes is discussed, and the mechanism of the diabetes is briefly considered.

5. We conclude that phaeochromocytoma should be suspected in any diabetic patient with severe hypertension, and in any hypertensive diabetic with unusual symptoms.

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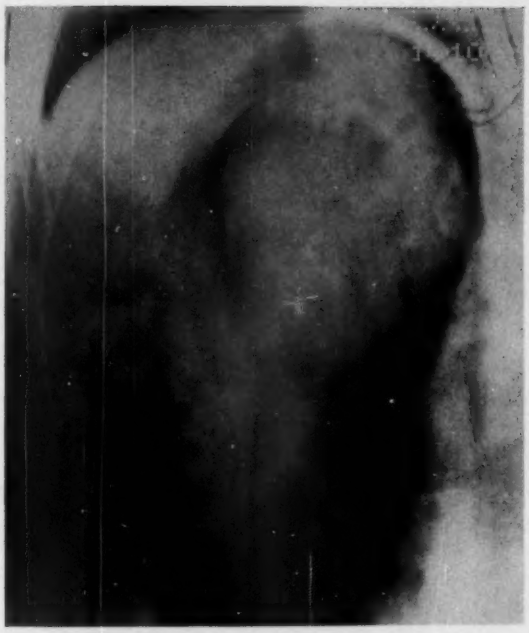

FIG. 4. Radiograph taken after presacral oxygen insufflation, showing right-sided phaeochromocytoma (Case 1)

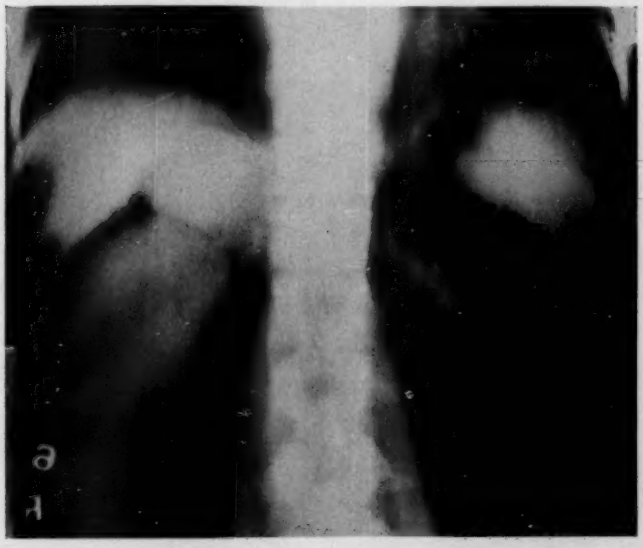

FIG. 5. Radiograph taken after presacral oxygen insufflation, showing right-sided phaeochromocytoma (Case 4)

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FURTHER STUDIES OF AN EPIDEMIC OF EXANTHEM ASSOCIATED WITH ASEPTIC MENINGITIS[1]

By D. A. J. TYRRELL, R. R. LANE, and B. SNELL

(From the Virus Research Laboratory of the University of Sheffield, Lodgemoor Hospital, and a general practice at Bolsover, Derbyshire)

With Plate 33

It is well known that the pattern of disease is changing, in that some diseases are diminishing in frequency and severity while others are on the increase. We wish to describe our experience of a syndrome, apparently caused by a virus, which became prevalent for the first time in 1956 in Western Europe and North America. We have already published some data in a preliminary form (Tyrrell and Snell, 1956).

Neva, Feemster, and Gorbach (1954) and Neva (1956) described summer epidemics in the United States of a disease which they named Boston exanthem, with a measles-like rash, lymphadenopathy, and mouth lesions. They saw no patients with aseptic meningitis in either of the epidemics they studied. Crawford, Macrae, and O'Reilly (1956) saw cases in London in 1954 in which there was a maculo-papular rash closely resembling that described by Neva, Feemster, and Gorbach (1954); in these cases there were increased cells and protein in the cerebrospinal fluid, though there were no signs of meningism. Before 1956 there were scattered outbreaks of an exanthem associated with aseptic meningitis (*Monthly Bulletin*, 1956), but in that year there were extensive outbreaks in the Midlands (Rotem, 1957), Wensleydale (Pickles, 1956), and East Anglia (Garnett, Burlingham, and van Zwanenberg, 1957), and also in Germany (Lennartz, Maass, and Kersting, 1957, Hennessen, 1957), Belgium (Nihoul and Quersin-Thiry, 1957), Toronto, Canada (LaForest, McNaughton, Beale, Clarke, Davis, Sultanian, and Rhodes, 1957), and Iceland (Sigurdsson, 1957). From many of these outbreaks viruses were readily isolated in tissue cultures of kidney-cells, and these viruses have all been neutralized by immune serum prepared against ECHO virus type 9. The virus isolated by Crawford, Macrae, and O'Reilly (1956) was also neutralized by this serum. Similar viruses have been isolated from outbreaks of aseptic meningitis in East Anglia (McLean and Melnick, 1957) and Darlington, England (Tyrrell, unpublished), and in Italy (Archetti, Felici, Russi, and Fua, 1956; Rita, Russi, and Fischer-Fantuzzi, 1956) and Switzerland (Baumann, Barben, Marti, Hassler, and Krech, 1957). The difference in the

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clinical picture described by different observers may be partly due to the differences in selection of cases (for example, by severity in the case of patients admitted to hospital), and also to diagnostic selection when a large proportion of patients seen were not tested for virus infection. Only the general practitioner, if he sees enough cases, is in a position to recognize the full range of clinical manifestations. It nevertheless seems possible that rashes have been much more prominent in some outbreaks than in others.

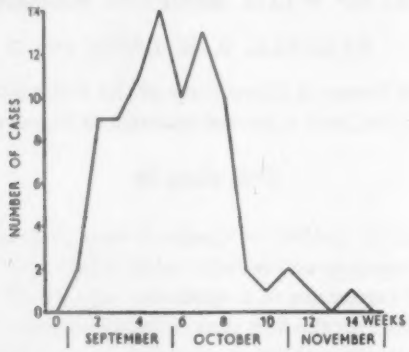

FIG. 1. Weekly totals of cases of characteristic illness seen in a practice of about 3,500.

Epidemiological Observations

The small section of this widespread epidemic which we studied occurred mainly in the practice of one of us (R. R. L.) in a mixed mining and rural area about 15 miles south of Sheffield. Patients were seen suffering from a febrile illness, alimentary symptoms, and a severe headache, and many developed a macular rash, with or without signs of meningitis. Eighty-five cases were seen between September and November, 1956, in a practice numbering about 3,500 persons. Fig. 1 shows the rise and fall of incidence. There were only eight adult patients, and nearly all the others were children under 10 years of age. As the disease was mild, and became well known in the neighbourhood, it is certain that many more recognizable cases occurred than were seen by us. Mothers often did not call the doctor when, after the diagnosis of the first case in their own family or that of a neighbour, one child after another became ill. We estimate that the disease affected at least one person in 20 of those included in the practice, and therefore a large proportion of the children under 10 years of age.

Virus studies were carried out in 11 affected families. In nine of these families there was evidence that one or more sick persons were infected with a Coxsackie A virus (Tyrrell and Snell, 1956), which was found in addition to be serologically related to ECHO virus type 9 (McLean and Melnick, 1957; Boissard, Stokes, Macrae, and MacCallum, 1957). A further analysis was made of the illnesses in the above nine families, and in three additional families from which the virus was isolated. In four families there was one case only, and in eight there were

from two to five cases. In the 12 families there were 37 children under 14 years of age, and 30 of these were ill. The secondary attack rate was 18/25, or 0·72, in this age group, and 6/28, or only 0·21, in persons of 14 years and over. Five persons, four children and one adult, were admitted to hospital. There were no deaths. The cases were divided equally between the sexes. In the same families the infection interval was determined, where an accurate history was available.

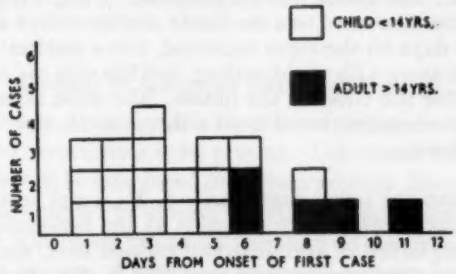

FIG. 2. The interval between the onset of the first and subsequent cases in 12 families in which virus was isolated from one or more persons. Adults were affected later than children.

This interval, the time between the onset of the first case and that of subsequent cases, was found to be much longer in the parents than in the children, as is shown in Fig. 2. It was presumed that the parents became infected from the children. It was not possible to make an accurate estimate of the incubation period.

These results show that, both in the epidemic as a whole and in those family outbreaks which were shown to be associated with a virus, the disease mainly affected children. It is of interest that of six unaffected adult contacts tested four had no detectable neutralizing antibody in the serum. We tested faeces from two such adults who were without detectable antibody, and no virus was found in either of them. This may be either because the test for antibodies was insufficiently sensitive, or because some factor other than antibody can prevent infection of the alimentary tract in adults, as has apparently been demonstrated with attenuated poliomyelitis viruses in experimental infections of man (Dane, Dick, Fisher, Connolly, and McKeown, 1957).

Representative Case Histories

The range of clinical patterns presented by the illness can best be illustrated by describing the four main types of case which were recognized.

1. *Short indeterminate illness* (*12 cases seen*). T. W., a girl of 10 years, awoke one morning with a headache and malaise. There were no other symptoms, and no abnormal physical signs. She remained in bed for three days, and had recovered completely in one week. A throat swab taken on the second day of disease yielded a virus, and during the illness there was a rise in titre of virus-neutralizing antibody from 16 to 256.

2. *Rash* (*12 cases seen*). S. T., a boy aged one year, became irritable and refused food one afternoon. The following day a few purplish-red macules were present on his face. The rash rapidly became blotchy, and spread, so that by the fourth day it extended over the face, trunk, and buttocks (Plate 33, Figs. 4 and 5). The larger lesions were slightly raised. By the third day his appetite had returned. There was no stiffness of the neck or mouth lesions. The cervical lymph-nodes were enlarged, and the left inguinal nodes were palpable and tender. The spleen was not palpable. A slight rhinorrhoea, present at the onset, had now increased to a moderate mucopurulent discharge. During the fifth and sixth days all the signs regressed, but a residual rash persisted on the face as purplish areas with slight scaling, and the skin did not appear normal until two weeks after the onset of the illness. The child remained irritable for several weeks. Virus was recovered from a throat swab and faeces collected on the third day of illness.

3. *Rash and meningitis* (*seven cases seen*). S. E., a girl aged three years, had a transient, mild upper-respiratory infection at the beginning of October. On October 11 she complained of headache and refused food, and in the afternoon vomited three times; the temperature was 103° F. On the following day the headache was more severe; she also complained of pain in the abdomen and left groin, and vomited or retched every 15 minutes, but had no diarrhoea. There was a fine macular rash on the face, and the cheeks were flushed. There were no mouth lesions. The cervical lymph-nodes were enlarged, and there were tender glands in the left groin. There was moderate stiffness of the neck and back. She improved rapidly, and by October 14 she was out of bed, although the rash was still present. On October 15 she had a recurrence of severe headache, but by October 17 both headache and rash had gone, and she made an uneventful recovery. A virus was recovered from a throat swab taken on October 12.

4. *Meningitis* (*three cases seen*). C. R., a nine-year-old girl, rapidly became ill with thirst, retrosternal pain, and severe frontal headache. On the following day the headache was more intense, and she began to vomit frequently. On admission to hospital on the third day she had a low fever (99° F), and slight stiffness of the neck and back. No other abnormal neurological signs were present. There were several small white spots on the buccal mucous membrane on both sides opposite the upper molar teeth, and the anterior cervical (angular) and inguinal lymph-nodes were palpable. Cerebrospinal fluid taken on admission showed an increase in lymphocytes and protein. The patient made a rapid recovery, and was well within 10 days, the mouth lesions and meningism having completely gone.

5. There was one patient in whom the illness took a more severe course, and the clinical picture suggested a 'toxic' state or mild encephalitis. C. W., a coal-miner aged 40 years, was the father of five children, four of whom were ill with a rash and headache. He had fluctuating severe headaches for four days, after which he had to give up work and go to bed, complaining of sleepiness, sore throat, and generalized aching. On examination he was very ill, drowsy, and sweating, with a temperature of 101° F. He had difficulty in answering questions owing to disorientation in time and sluggishness of thought. Neck stiffness and Kernig's sign were present. The reflexes were normal apart from absent upper abdominal responses. The changes in the cerebrospinal fluid are shown in Table II. The inguinal and axillary glands were slightly enlarged. The abdomen was somewhat distended. There was a faint blotchy erythema over the upper

trunk, and the face was flushed. Moderate conjunctival injection was present. The lips were dry. The tongue was furred, and the buccal mucous membrane was oedematous, and showed numerous small white dots and small painless ulcers around the papillae of Stensen's ducts (Plate 33, Fig. 6). Seventeen days after the onset of illness he was completely well, and the mouth lesions had disappeared. Although there was no clinical evidence of meningeal irritation, the cerebrospinal fluid was still abnormal. Nose and throat swabs taken on the sixth day of disease yielded no virus, but there was a rise in antibody titre, as shown in Table II.

Analysis of Symptoms and Clinical Signs

Clinical records were available for 32 cases occurring in the 12 families in which virus infection was known to be present. The overall frequency of certain symptoms and signs can be calculated from these records. The relative frequency of the symptoms and signs was almost the same in the 19 patients from whom virus was isolated. The onset was usually rapid, and the illness lasted from two to 15 days, with an average of 5·5 days. Of the 12 patients whose temperatures were taken shortly after the onset, there was fever in 11, and in three of these patients it reached 103° F. All patients old enough to do so complained of headaches, often severe and not relieved by mild analgesics. In young children they were accompanied by irritability. Twenty patients complained of alimentary symptoms at the onset of the illness: 15 vomited, and two had nausea only; in five cases there was abdominal colic, and two had mild diarrhoea. In one patient the abdomen was tender. Nineteen of 32 patients gave a history of a rash, which was confined to the face in four of the 13 cases in which it was seen. Nineteen patients were examined during the acute phase of the disease; six of these had definite mouth lesions like those shown in Plate 33, Fig. 6, 10 had stiffness of the neck, and in seven mild lymphadenopathy was found. In 16 cases there was one bout of illness and an uninterrupted recovery. In 13 cases the illness was diphasic and, where the temperature records were available, the two bouts of illness corresponded to two periods of fever. In three cases the illness was triphasic, and in one there was no adequate history of the course of the disease. Some patients suffered from lassitude, minor headaches, or muscular aches for several weeks after the acute phase of the illness was past. It was difficult to get exact details of these late complaints.

Results of Virus Studies

One type of virus was recovered from the whole epidemic. This was a Coxsackie A virus, serologically closely related to ECHO virus 9, and will be fully described elsewhere. An adenovirus strain was isolated from one boy, who had been ill a week previously. Fig. 3 shows the relation between the day of disease on which specimens were collected and the results of attempts to isolate virus from the specimens. It will be seen that there was a period during the first six days of the illness when virus could be recovered. After that period virus

disappeared from the throat, and a few days later from the faeces also. In order to determine whether virus was regularly associated with the disease, specimens were collected (at about the same time as those from patients) from members of the families who were not ill, and also from patients in the hospital who had acute nervous disorders, other than the type of aseptic meningitis just described. The results of these studies are summarized in Table I. This shows that virus infection was found almost exclusively in overt cases of the illness. In addition,

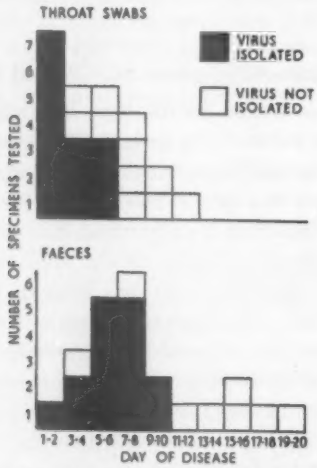

FIG. 3. A summary of the results of examining throat swabs and faeces from 35 patients for the presence of virus. Specimens collected late in the disease yielded no virus.

sera were tested for the presence of neutralizing and complement-fixing antibodies. The results of these tests are also shown in Table I, and indicate that antibody was found in sera from patients in the epidemic more frequently than in sera from control persons and in a miscellaneous group of sera from persons of all ages. It was also desirable to show that patients had undergone an infection during the acute phase of the illness, particularly because some viruses are excreted for prolonged periods. Sera were collected from all hospital patients, and from a few seen at home. A rise in neutralizing antibodies in 10 of 14 patients indicated that the illness was associated with actual infection. The remaining four patients had unchanging levels of antibody. Table II shows the results of all the virus studies of patients seen in hospital. Sera from persons not suffering from the disease had either no antibodies or unchanging levels of antibody. None of 14 hospital patients with a rash or aseptic meningitis studied in November and December showed evidence of infection with the same virus. Table II also shows the results of routine laboratory tests in patients seen in hospital. Blood and urine examinations gave substantially normal results, but there was a regular increase of cells in the cerebrospinal fluid, and usually a rise

in protein concentration. The sugar and chlorides in the cerebrospinal fluid were normal.

Other Outbreaks Studied

One of the patients studied (T. O'C.) became ill in Nottingham, where there was a large outbreak of a disease with rash and meningitis, called therefore 'Nottingham meningitis' (Dodd, 1956). The clinical and laboratory findings in her case were identical with those seen in cases occurring closer at hand. We

TABLE I

Results of Tests for Virus and for Antibody in Patients and Control Groups

	Virus present in		*Neutralizing antibody present in serum*
	throat swab	*faeces*	
Family study:			
Patients (including 5 treated in hospital) .	12/21*	9/15	7/7
Controls	0/12	1/5	1/5
Hospital study:			
Patients (including 5 from family study) .	3/6	4/7	7/7
Controls	0/4	†2/10	8/15
Miscellaneous sera	..	..	35/79

* Numerator = number positive; denominator = number tested.

† One case of pure aseptic meningitis, and one of seasonal papular urticaria and aseptic meningitis.

received paired sera from nine patients seen in the practice of Dr. W. H. Lyle of Newton-le-Willows, Lancashire. All contained antibody against ECHO virus type 9, and five showed a rising titre on complement-fixation tests. These cases were clinically representative of those seen by Dr. Lyle (Lyle, 1956*a*). No virus, however, was isolated; and no antibodies were detected in specimens sent from similar cases, with a rash and involvement of the nervous system, seen in Lowestoft in 1956 by Dr. M. Carter.

Discussion

We have described an epidemic of cases of febrile illness with a maculopapular rash, aseptic meningitis, and lesions of the buccal mucous membrane. The disease was clinically very variable—a fact realized only because family epidemics were studied as well as patients in hospital. We know of no accounts of an epidemic of this type occurring before the last few years. Individual cases, however, could not have been recognized as a specific infection in the absence of an epidemic. The rashes might have been labelled as rubella or atypical rubella; or perhaps, if they had occurred in summer and the child had shown alimentary symptoms, they would have been diagnosed as heat rash or food rash. Lymphadenopathy, fever, and rash might suggest infectious mononucleosis. The only clinical diagnosis in cases with meningism alone would be aseptic meningitis or non-paralytic poliomyelitis. Cases with meningitis and rash should, however, have been distinguishable from leptospirosis or meningococcal infections. Small mouth ulcers might readily have been overlooked or

TABLE II

Summary of Laboratory Findings in Nine Hospital Patients shown to be Infected with the Virus

					Cerebrospinal fluid			Virus isolation			Antibody titres		
					Cells							Complement-fixing	
Patient	*Age (years)*	*Sex*	*Type of illness*	*Collected on day of disease*	*no. per cu. mm.*	*% lymphocytes*	*Protein (mg./100 ml.)*	*Throat*	*Faeces*	*Cerebrospinal fluid*	*Neutralizing*	*Mouse‡*	*Tissue culture‡*
G. H.*	6	M	Rash and meningitis	2	100	*c.* 80	80	+	+	n.s.	< 8/1,024†	< 4/20	< 4/40
P. W.	12	F	Rash and meningitis	5	1,250	*c.* 80	70	0	0	0	32/512	< 4/< 4	< 4/16
T. O'C.*	9	F	Rash and meningitis	3	393	89	35	n.s.	+	n.s.	16/256	8/128	< 4/256
P. B.	7	M	Rash and meningitis	5	*c.* 50	100	35	0	+	+	< 8/2,048	16/128	4/128
J. B.	8	M	Meningitis	5	400	80	65	n.s.	0	n.s.	128/1,024	< 4/< 4	< 4/8
D. K.*	3	M	Meningitis	3	400	60	70	n.s.	+	n.s.	n.s./128	n.s./64	n.s./96
C. R.*	9	F	Meningitis	3	104	100	70	+	+	n.s.	> 512/2,048	8/8	8/32
C. W.	40	M	Meningitis with mild encephalitis. Rash	4	1,584	75	90	0	n.s.	0	128/512	< 4/8	< 4/< 8
				9	200	83	75						
				16	100	100	60						
H. B.	7	F	Rash	..	n.s.	..	..	+	+	n.s.	256/1,024	8/n.s.	96/n.s.

* The family was not studied in these cases.

† The figure before the line is the titre of acute-phase serum, and the figure after the line that of convalescence.

‡ Source of antigen.

n.s. = no specimen available.

regarded as non-specific, or confused with the Fordyce spots seen in normal persons. Similar lesions near the fauces occur in the disease herpangina produced by certain Coxsackie A viruses (Beeman, 1954). Cases of headache, sore throat, fever, and malaise correspond to the syndrome of summer grippe which can also be produced by Coxsackie viruses (Walton and Melnick, 1953).

Some of our patients showed minor changes in the reflexes, such as those found by Karzon, Barron, Winkelstein, and Cohen (1956) in patients infected by ECHO virus type 6. One of our patients had mild encephalitis, and another had transient difficulty in commencing micturition. Lyle (1956*b*) saw reflex changes, and also nerve deafness, in some of his cases. It is therefore probable that this virus and other ECHO viruses can damage more of the human nervous system than the meninges. Nevertheless it seems unlikely that it was responsible for the outbreaks of meningoencephalomyelitis which have been described recently (*Lancet*, 1956). It is also interesting that Lyle (1956*b*) has seen adult cases of acute myositis associated with typical illness in children. This suggests that this particular Coxsackie A virus may attack striated muscle in man; and certainly aching and stiffness of muscles, and fatigue in convalescence, were troublesome features in some of our adult patients. Coxsackie B viruses are well known to cause the acute myositis of Bornholm disease.

The virus isolated by Neva, Feemster, and Gorbach (1954) has been found to be the same serologically as a virus isolated from cases of aseptic meningitis in Boston and now designated ECHO virus type 16 (F. A. Neva and J. L. Melnick, 1957; personal communications). There is evidence that some other ECHO virus strains are associated with epidemics of aseptic meningitis (Karzon, Barron, Winkelstein, and Cohen, 1956), but many of the prototype ECHO viruses, including type 9, were found in the faeces of healthy children (Committee on ECHO Viruses, 1956). Therefore it has been wisely written that 'the association between virus excretion, infectivity and symptomatology can be established only when significant numbers of individuals are studied, correlating virus excretion, appearance of antibodies and development of symptom patterns in virus carriers and their contacts as well as in non-infected control populations' (Honig, Melnick, Isacson, Parr, Myers, and Walton, 1956). We feel that the combined clinical and laboratory studies presented here show that the epidemic we observed was caused by the virus we isolated. This view is supported by the fact that the same virus was recovered from similar cases in many parts of the Western world at about the same time.

This is the first time that it has been possible to incriminate any enteric virus as the cause of a rash and widespread lymphadenopathy, although it is known that poliomyelitis viruses invade the blood-stream and lymphatic tissue of man, and classic descriptions of poliomyelitis refer to rash and lymphadenopathy in that disease (Peabody, Draper, and Dochez, 1912). There is one case, reported by Kilbourne and Goldfield (1956), which could have been an instance of rash and meningoencephalitis caused by a Coxsackie A 9 virus. It seems to us that the syndrome we have described, which can probably be produced by more than one enteric virus, should be given a descriptive title. We put forward for

discussion 'benign exanthematous virus meningitis'. 'Meningitis of virus origin' (Rotem, 1957) is too indefinite, and 'meningoencephalitis' (Lyle, 1956*a*) suggests a connexion with a different clinical syndrome.

We wish to thank Dr. J. Kennedy, Professor R. S. Illingworth, Dr. J. B. McKay, Dr. J. W. Dent, and Dr. H. O. Hughes, for permission to examine patients under their care, and Mr. P. Ramsbottom for technical assistance. The work was supported in part by the National Fund for Poliomyelitis Research. Photographs were taken by the Photographic Department of the United Sheffield Hospitals.

Summary

We have observed an epidemic of a febrile disease with headache, involving at least 85 patients in a practice of about 3,500. Many patients had a maculopapular rash, lymphadenopathy, aseptic meningitis, and lesions of the buccal mucous membrane, either separately or in combination. Vomiting was a common initial symptom, and some adults complained of myalgia. The disease was benign, but convalescence was sometimes rather long. The disease affected children under 10 years of age and their parents.

Thirty-three strains of virus were isolated, and rising antibody titres were demonstrated by three separate methods in 10 out of 14 cases. Similar studies of control patients gave negative results, and it was concluded that the virus was associated with all forms of the disease, and probably caused it. The viruses were of identical type, and related to Coxsackie group A viruses and ECHO type 9 virus. These results are similar to those of other workers; but we have also studied single cases, and a small outbreak of rash and meningitis, occurring since this epidemic, and found there was no evidence of the presence of this virus.

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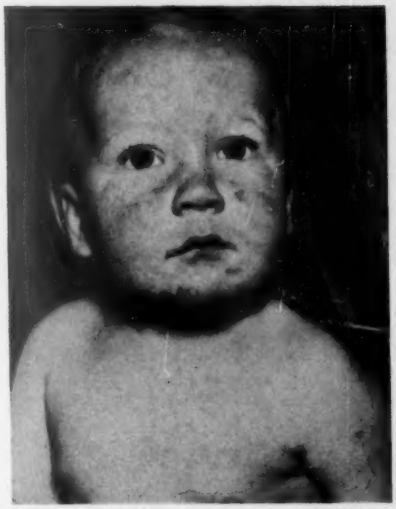

FIG. 4. Case 2. The rash on the face on the fourth day of the disease. Note the blotchy appearance

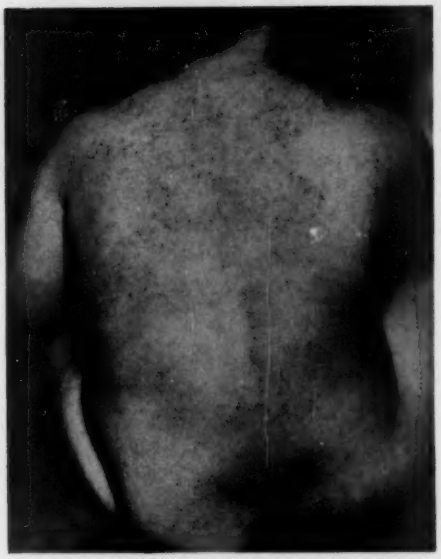

FIG. 5. Case 2. The rubella-like rash on the back on the fourth day of the disease

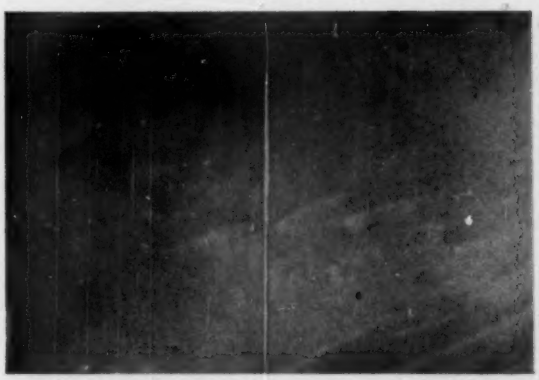

FIG. 6. Case 5. An ulcer and several small lesions in the mucous membrane below the parotid duct on the twelfth day of the disease

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OBSERVATIONS ON THE PERIPHERAL CIRCULATION IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY[1]

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With Plates 34 to 37

An association between clubbing of the fingers and chronic pulmonary disease has been recognized since Hippocrates (*c.* 400 B.C.) commented on the curved finger-nails of a patient with empyema. Many centuries later, when the syndrome of hypertrophic pulmonary osteoarthropathy was first described, it was realized that intrathoracic disease and gross clubbing could be further complicated by painful and swollen joints, and by a periosteal reaction in the shafts of the long bones (Bamberger, 1889, 1891; Marie, 1890). With adequate treatment of the primary pulmonary lesion, pain and swelling were relieved and newly formed bone was resorbed. Similar changes in the bones and joints have been described in the course of extrapulmonary disease, generally in association with hepatic lesions (Locke, 1915; Mendlowitz, 1942; de Meyer and Sarasin, 1950), and also in patients with no evidence of primary pulmonary or hepatic disease (Camp and Scanlan, 1948; Keats and Bagnall, 1954). In the absence of post-mortem studies, however, the nature of the peripheral lesions in such cases and their precise relationship to pulmonary osteoarthropathy remain unknown.

Among the many theories advanced to explain the mechanism by which pulmonary disease induces such changes in the extremities (Bamberger, 1891; Marie, 1890; Mendlowitz, 1942), that of a circulatory disturbance has been the most frequent (Mauer, 1947; Mendlowitz, 1942, 1954; Semple and McCluskie, 1955). An increased vascularity of the terminal phalanges has been demonstrated in clubbed fingers associated with a variety of lesions, but not in cases of congenital clubbing (Charr and Swenson, 1946; Lovell, 1950; Mendlowitz, 1938, 1941; Wilson, 1952). Quantitative studies of the peripheral circulation in cases of osteoarthropathy, however, are scanty, and the results to some extent contradictory; thus in three patients the blood-flow through the finger-tips was considered to lie within the normal range (Mendlowitz, 1941), but measurements of hand blood-flow in one patient provided evidence of an increase in peripheral flow (Logan, Marshall, Shepherd, and Whelan, 1954). The present investigation was therefore undertaken in an attempt to determine whether the peripheral circulation in cases of osteoarthropathy differed in any way from normal. The

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TABLE I

Clinical Findings, Laboratory Investigations, and Results of Treatment in 18 Patients with Hypertrophic Pulmonary Osteoarthropathy

Case number	*Age (years)*	*Duration of joint symptoms (years)*	*Duration of other symptoms (years)*	*Blood-pressure (mm.Hg)*	*Erythrocyte sedimentation rate (mm./hr.)*	*Serum alkaline phosphatase (King-Armstrong units)*	*Special features*	*Bronchoscopic findings*	*Radiographs*		*Treatment and subsequent course*	*Diagnosis*
									Chest	*Bone*		
1	67	2	2	130/80	68	14·0	Haematemesis; gynaecomastia; urinary oestrogens increased	Normal	Large mass L. upper lobe	Periosteal changes +++ in humeri, radii, ulnae, femora, tibiae, fibulae, metatarsals, metacarpals	Inoperable. Died 2 months after diagnosis	Carcinoma of bronchus; histology not determined
2	61	4/12	4/12	130/80	..	..	..	Growth in R. main bronchus	Cavitated lesion R. lower lobe	Periosteal changes in tibiae and fibulae only	Thoracotomy; inoperable. Died 3 months later	Carcinoma of bronchus (squamous)
3	56	3/12	3/12	140/85	68	..	..	Concentric stenosis of R. upper-lobe bronchus	Massive opacity R. upper lobe	Periosteal changes in tibiae, fibulae, ulnae	Palliative lobectomy. Vagotomy. Died 2 months later with cerebral metastases	Carcinoma of bronchus (adenocarcinoma)
4	72	7/12	7/12	140/70	..	..	Bowel symptoms	Narrowing of L. lower-lobe bronchus	Consolidation L. lower lobe	Periosteal changes +++ in radii, ulnae, femora, tibiae, fibulae, metatarsals, metacarpals	L. pneumonectomy and vagotomy; immediate relief of joint pains; recurred 2 months later. Metastases in R. lung, liver, &c.	Carcinoma of bronchus (adenocarcinoma)
5	45	3/12	6/12	130/90	..	..	Recent coronary thrombosis	Normal	Small round tumour L. upper lobe	Periosteal changes in femora, tibiae, fibulae, metatarsals	L. upper lobectomy. Joint pains relieved. Glandular metastases. Abdominal symptoms. Deep X-rays	Carcinoma of bronchus (squamous)
6	51	3/12	3/12	120/80	121	9·0	Superior venacaval obstruction	R. upper-lobe orifice narrowed	Massive opacity R. upper lobe	Periosteal changes +++ in femora, tibiae, fibulae, radii, ulnae	Thoracotomy; inoperable. Died 3 days later	Carcinoma of bronchus (columnar)
7	57	6/12	14/12	110/70	40	..	History of 'rheumatism' for 14 years. Urinary oestrogens increased, but no gynaecomastia	..	Cavitated lesion R. middle lobe	Periosteal changes ++ in tibiae, fibulae, femora; less marked in metatarsals, radii, ulnae	R. middle lobectomy. Immediate relief of joint pain. Urinary oestrogens within normal range after operation	Carcinoma of bronchus (undifferentiated)

8	57	$\frac{0}{12}$	$\frac{11}{12}$	110/75	112	7·0	Severe pain from spinal metastases	Widening of carina. Irregular mucosa in L. lateral basal bronchus	Circumscribed dense opacity L. lower lobe	Periosteal changes in tibiae, fibulae, metatarsals, metacarpals. Metastases in femora and humeri	Inoperable. Limb and back pains partially relieved by salicylates, then by cortisone. Metastases in R. lung, kidney, adrenals, ribs, femur, spine, &c.	Carcinoma of bronchus (adenocarcinoma)
9	53	$\frac{0}{12}$	3	170/95	..	..	Gynaecomastia. Oedema of legs +	Normal	Cavitated lesion R. upper lobe	Periosteal changes in tibiae, fibulae, radii, ulnae, metacarpals	R. upper lobectomy. Immediate relief of oedema and pain. Gradual regression of radiological bone change. Died 9 months later with cerebral metastases	Carcinoma of bronchus (adenocarcinoma)
10	53	$\frac{0}{12}$	$\frac{0}{12}$	110/90	48	10·4	L. recurrent laryngeal involvement	L. recurrent laryngeal palsy	Peripheral lesion ant. segment L. upper lobe. Hilar involvement	Periosteal changes in tibiae, fibulae, radii, ulnae, metacarpals	Deep X-rays. Joint pains relieved; general condition deteriorated rapidly. Died 1 month later with cerebral deposits	Carcinoma of bronchus (poorly differentiated squamous-cell)
11	43	$\frac{7}{12}$	$\frac{0}{12}$	130/90	..	..	Gynaecomastia	Normal	Large peripheral lesion L. upper lobe	Periosteal changes in femora, tibiae, fibulae, radii, ulnae	L. pneumonectomy. Immediate relief of joint symptoms. Died 7 months later with cerebral metastases	Carcinoma of bronchus (adenocarcinoma)
12	51	$\frac{0}{12}$	$\frac{0}{12}$	140/98	42	..	Pain in temporomandibular joints	Elevation of floor of R. upper lobe	Large irregular mass R. upper lobe	Periosteal changes +++ in humeri, radii, ulnae, metacarpals, femora, tibiae, fibulae, metatarsals	R. pneumonectomy. Immediate relief of joint symptoms. Slow regression of radiological bone change. Alive and well 20 months later	Carcinoma of bronchus (polygonal-cell)
13	63	$\frac{0}{12}$	$\frac{0}{12}$	125/95	63	8	Gynaecomastia	Normal	Opacity apex R. lower lobe	Periosteal changes in tibiae and fibulae	R. pneumonectomy. Immediate relief of joint pains. Gradual subsidence of gynaecomastia. Died 10 months later with (?) metastases in spine	Carcinoma of bronchus (undifferentiated)
14	59	1	18	95/70	132	..	..	No bronchoscopy	Bilateral basal bronchiectasis	Periosteal changes in femora, tibiae, fibulae, radii, ulnae	Chronic bronchitis and bronchiectasis. Cor pulmonale; death	Bronchiectasis

Case number	Age (years)	Duration of joint symptoms (years)	Duration of other symptoms (years)	Blood-pressure (mm.Hg)	Erythrocyte sedimentation rate (mm./hr.)	Serum alkaline phosphatase (King-Armstrong units)	Special features	Bronchoscopic findings	Radiographs: Chest	Radiographs: Bone	Treatment and subsequent course	Diagnosis
15	32	$\frac{8}{12}$	13	150/90	60	..	..	No bronchoscopy	Cystic bronchiectasis L. lower lobe, lingula, R. middle lobe	Periosteal changes in tibiae and fibulae	L. pneumonectomy. Died shortly after operation	Bronchiectasis
16	70	$\frac{8}{12}$	$\frac{9}{12}$	130/95	..	..	Gross oedema feet to knees	No bronchoscopy	Massive opacity L. chest; mediastinal shift to R.	Periosteal changes in tibiae, fibulae, radii, ulnae, metacarpals	Coarsely lobulated tumour, with numerous vascular adhesions to diaphragm, chest wall, under surface of lung, removed at thoracotomy. Immediate relief of symptoms. Rapid subsidence of oedema	Mediastinal fibroma
17	53	$\frac{11}{12}$	$\frac{11}{12}$	130/85	20	..	Initial attack of joint pain and swelling relieved by prostigmine	Normal	(?) Emphysematous bulla, (?) lung cyst, L. lower lobe	Periosteal changes in femora, tibiae, fibulae, radii, ulnae, metacarpals	..	(?) Lung cyst
18	62	$\frac{4}{12}$	$\frac{4}{12}$	180/90	..	..	Urinary oestrogens increased, but no gynaecomastia. Oedema ++ of legs	No bronchoscopy	Rounded peripheral opacity (retrocardiac) L. lower lobe	Periosteal changes ++ in tibae and fibulae. Minimal reaction in radii and ulnae	L. lower lobectomy. Immediate relief of pain; slow subsidence of oedema	Carcinoma of bronchus (adenocarcinoma)

circulation in the limbs was studied in patients in whom pulmonary disease was associated with clubbing of the digits and with radiological evidence of periosteal change in the long bones.

Patients Studied (Table I)

The 18 men with hypertrophic pulmonary osteoarthropathy were aged between 32 and 72 years. Osteoarthropathy was secondary to carcinoma of the bronchus in the majority (Cases 1 to 13 and 18); in the remainder the diagnosis was bronchiectasis (Cases 14 and 15), fibroma of the lung (Case 16), and (?) lung cyst (Case 17). Marked clubbing was present in all cases. In most instances the onset of swollen finger-tips had been noticed by the patients themselves, and in two men this was apparently the first sign of their illness (Cases 5 and 17). Swelling and pain in the wrists, ankles, knees, and other joints was an invariable complaint, and the presenting symptom in eight patients (Cases 1 to 4, 6, 12, 13, and 18). The duration of this complaint before admission varied from five weeks (Case 9) to two years (Case 1). In the two men with bronchiectasis, joint swelling developed late in the course of the disease, and arthropathy was only evident a few months before death. A history of intermittent pain and swelling in various joints, with freedom from both pain and deformity between acute episodes, was given by four patients (Cases 2, 4, 11, and 16). The onset of joint pain was generally associated with respiratory symptoms, such as cough (frequently the exacerbation of a chronic 'smoker's cough'), shortness of breath, or haemoptysis. X-rays of the limbs showed periosteal deposition of bone along the shafts of the long bones, which was always more extensive in the legs than in the arms. In three patients (Cases 2, 5, and 13) there was no radiological evidence of arthropathy in the upper limbs, and in two (Cases 15 and 18) periosteal change in the radius and ulna was very slight.

Gynaecomastia was present in four patients (Cases 1, 9, 11, and 13); oestrogen excretion was measured in Case 1, and found to be well above normal. Urinary oestrogens were also determined in two patients in whom there was no clinical evidence of gynaecomastia (Cases 7 and 18). The level of oestrogen excretion was initially high in both these patients, and fell after removal of the bronchial carcinoma. Urinary oestrogens were measured by the method of Brown (1955), as modified by Brown, Bulbrook, and Greenwood (1957). The erythrocyte sedimentation rate was greater than 20 mm. in one hour in all the 11 patients in whom it was determined. Serum alkaline phosphatase was measured in five cases: the values were within the normal range.

After removal of the primary chest lesion, which was possible in only 10 cases, joint pain and swelling were immediately relieved, but new periosteal bone was only gradually resorbed. Radiotherapy to the chest lesion relieved the joint symptoms in one patient (Case 10).

Methods

Limb blood-flow was measured by venous occlusion plethysmography under standard laboratory conditions; metal plethysmographs were filled with water kept at 33±1° C. for the hand, 34±1° C. for the forearm and foot, and 35±1° C. for the calf (Barcroft and Swan, 1953). Recordings were made at half-minute intervals for at least 30 minutes. Blood-flow was calculated and expressed in ml. per 100 ml. tissue per minute.

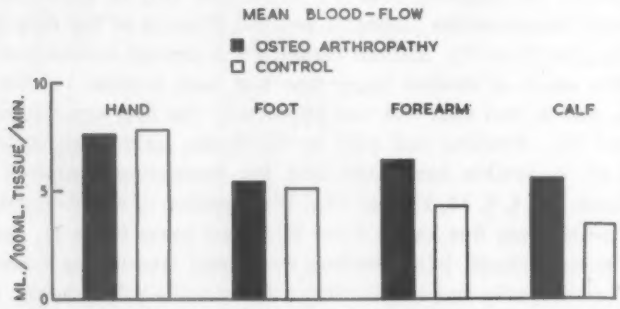

FIG. 1. Mean blood-flow (ml. per 100 ml. tissue per minute) in hand, foot, forearm, and calf, in patients with pulmonary arthropathy (solid rectangles), and in a control group (open rectangles).

Adrenaline (synthetic L-adrenaline tartrate) was given intravenously, in a dose of 10 μg. per minute for 10 minutes, during the course of a continuous intravenous infusion of saline (0·9 per cent. w/v NaCl solution). The potency of the adrenaline was maintained by adding 0·1 ml. of ascorbic acid to each pint of saline used in the infusions (Gaddum, Peart, and Vogt, 1949).

Changes in skin temperature during body cooling were recorded by means of copper-constantin thermo-couples connected to a galvanometer. Thermo-couple junctions were placed over fixed bony points, and also at definite distances from such points, so that the determinations before and after operation could be compared. Recordings were made, with the subjects at rest, for a period of 35 to 80 minutes.

A femoral arteriogram was performed under general anaesthesia in one subject (Case 6), 50 per cent. sodium acetrizoate being given by percutaneous puncture of the left femoral artery. The new periosteal bone was examined histologically in two specimens obtained *post mortem*: a portion of femur in Case 4, and a section from the tibia of a patient described by Lloyd (1957).

Peripheral circulatory studies were also made in patients with carcinoma of the bronchus in whom there was no evidence of arthropathy, and in healthy adults. Resting blood-flow and responses to intravenous adrenaline were similar in these two groups. Control data, as given in the tables, are mean values derived from this particular study.

TABLE II

Peripheral Blood-Flow in Patients with Hypertrophic Pulmonary Osteoarthropathy

	ml./100 ml. tissue/min.			
Case number	*Hand*	*Foot*	*Forearm*	*Calf*
1	2·1	6·1	5·6	10·3
2	..	..	15·6	2·0
3	..	..	4·2	4·6
4	7·3	7·4	9·9	11·0
5	10·7	2·1	2·5	3·8
6	11·8	12·5	8·4	4·3
7	9·0	3·4	3·5	2·3
8	..	..	6·0	5·4
9	..	..	5·5	7·9
10	..	..	7·9	4·8
11	..	..	8·8	6·0
12	..	5·1	..	4·9
13	9·4	..	4·6	7·6
14	5·4	3·6	3·6	3·8
15	..	..	4·8	6·5
16	..	5·7	3·8	..
17	5·4	3·0	7·9	3·1
18	..	..	5·9	6·6
Mean flow in osteo-arthropathy	7·6	5·4	6·4	5·6
Mean flow in control group	7·8	5·1	4·3	3·5

TABLE III

Effect of Intravenous Infusions of Adrenaline on Forearm Blood-Flow in Patients with Hypertrophic Pulmonary Osteoarthropathy

	ml./100 ml. tissue/min.			
Case number	*A*	*B*	*B−A*	$\left(\frac{B-A}{A}\right)\%$
1	5·7	7·9	+2·2	+39
4	9·4	13·9	+4·5	+49
5	2·4	7·2	+4·8	+200
6	8·5	9·2	+0·7	+8
7	3·8	3·8	0	0
8	6·0	7·5	+1·5	+25
9	4·7	4·6	−0·1	−2
10	6·8	5·3	−1·5	−22
11	8·8	9·6	+0·8	+9
14	3·6	4·1	+0·5	+14
15	4·7	7·9	+3·2	+68
17	8·8	11·4	+2·6	+30
18	5·7	8·6	+2·9	+51
Mean value in osteo-arthropathy	6·1	7·8	+1·7	+36
Mean value in control group	4·5	8·4	+3·4	+97

A = mean flow during the four minutes preceding the infusion of adrenaline (10 μg. per minute for 10 minutes).

B = mean flow during the last four minutes of the adrenaline infusion.

Results

Resting limb flow (Table II; Fig. 1). Each individual value in Table II is based on readings taken at half-minute intervals over a period of 15 to 30

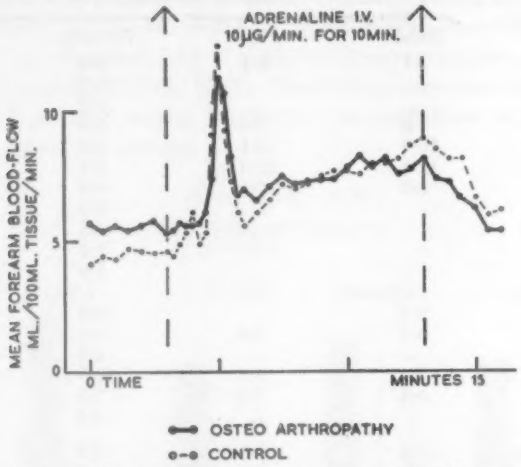

FIG. 2. Mean forearm blood-flow (ml. per 100 ml. tissue per minute) in patients with pulmonary arthropathy and in the control group before, during, and after the intravenous infusion of adrenaline (10μg. per minute for 10 minutes).

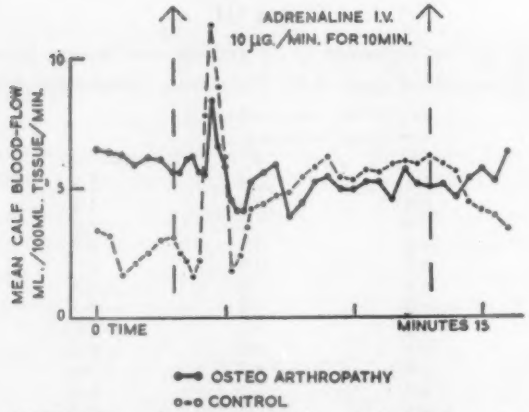

FIG 3. Mean calf blood-flow (ml. per 100 ml. tissue per minute) in patients with pulmonary arthropathy and in the control group before, during, and after the intravenous infusion of adrenaline (10μg. per minute for 10 minutes).

minutes. Hand blood-flow averaged 7·6 ml. in the patients with arthropathy, and 7·8 ml. in the control group; the corresponding mean values for foot blood-flow were 5·4 ml. and 5·1 ml. respectively. The mean flow in the hands and feet of patients with osteoarthropathy was therefore very close to the level

TABLE IV

Effect of Intravenous Infusions of Adrenaline on Calf Blood-Flow in Patients with Hypertrophic Pulmonary Osteoarthropathy

Case number	ml./100 ml. tissue/min. A	B	B−A	$\left(\frac{B-A}{A}\right)\%$
1	10·2	7·7	−2·5	−25
4	11·0	5·2	−5·8	−53
5	4·0	2·8	−1·2	−30
6	4·5	4·5	0	0
7	2·4	2·6	+0·2	+8
8	5·7	5·6	−0·1	−2
9	7·1	5·0	−2·1	−30
10	4·8	4·6	−0·2	−4
11	6·0	6·8	+0·8	+13
12	5·1	3·7	−1·4	−27
14	4·3	2·4	−1·9	−44
15	6·5	6·3	−0·2	−3
17	2·7	1·7	−1·0	−37
18	9·7	8·3	−1·4	−14
Mean value in osteo-arthropathy	6·0	4·8	−1·2	−18
Mean value in control group	3·7	6·2	+2·6	+75

A = mean flow during the four minutes preceding the infusion of adrenaline (10 μg. per minute for 10 minutes).
B = mean flow during the last four minutes of the adrenaline infusion.

TABLE V

Effect of Intravenous Infusions of Adrenaline on Forearm Blood-Flow in Patients with Hypertrophic Pulmonary Osteoarthropathy Before and After Operation

Case number	ml./100 ml. tissue/min. A	B	B−A	$\left(\frac{B-A}{A}\right)\%$
(i) *Before operation*				
7	3·8	3·8	0	0
9	4·7	4·6	−0·1	−2
10	6·8	5·3	−1·5	−22
11	8·8	9·6	+0·8	+9
18	5·7	8·6	+2·9	+51
Mean	6·0	6·4	+0·5	+7
(ii) *After operation*				
7	4·8	10·1	+5·3	+110
9	2·1	5·7	+3·6	+171
10	2·7	5·7	+3·0	+111
11	2·2	5·2	+3·0	+136
18	5·1	14·1	+9·0	+176
Mean	3·0	8·1	+4·8	+141

A = mean flow during the four minutes preceding the infusion of adrenaline (10 μg. per minute for 10 minutes).
B = mean flow during the last four minutes of the adrenaline infusion.

recorded in the control series. The mean forearm flow in patients with osteo-arthropathy was 6·4 ml., compared with 4·3 ml. in control subjects; calf blood-flow averaged 5·6 ml. in subjects with arthropathy, and 3·5 ml. in the control

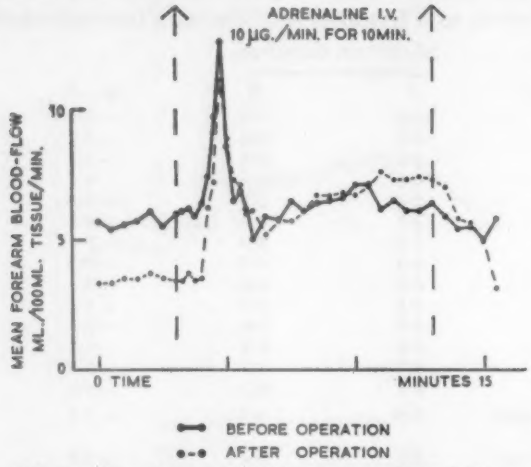

FIG. 4. Mean forearm blood-flow (ml. per 100 ml. tissue per minute) in patients with pulmonary arthropathy before operation and after operation, before, during, and after the intravenous infusion of adrenaline (10 µg. per minute for 10 minutes).

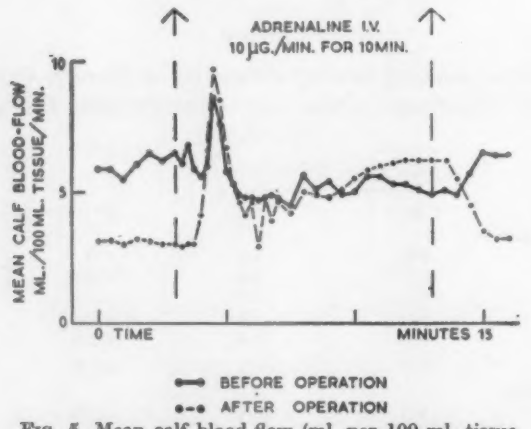

FIG. 5. Mean calf blood-flow (ml. per 100 ml. tissue per minute) in patients with pulmonary arthropathy before operation and after operation, before, during and after the intravenous infusion of adrenaline (10 µg. per minute for 10 minutes).

group. Thus, in the patients with hypertrophic pulmonary osteoarthropathy, the mean flow in both forearm and calf was about one and a half times as great as that recorded in the control group.

Effect of intravenous adrenaline (Tables III and IV; Figs. 2 and 3). The mean

flow in forearm and calf during the four minutes immediately before the infusion of adrenaline was compared with the mean flow during the last four minutes of this infusion, and the change in flow induced by adrenaline has been expressed as a percentage of the resting level of flow. In patients with osteoarthropathy forearm blood-flow increased on average by 36 per cent. during an intravenous infusion of adrenaline; the corresponding change in the control

TABLE VI

Effect of Intravenous Infusions of Adrenaline on Calf Blood-Flow in Patients with Hypertrophic Pulmonary Osteoarthropathy Before and After Operation

	ml./100 ml. tissue/min.			
Case number	*A*	*B*	*B−A*	$\left(\frac{B-A}{A}\right)\%$
(*i*) *Before operation*				
7	2·4	2·6	+0·2	+8
9	7·1	5·0	−1·9	−27
10	4·8	4·6	−0·2	−4
11	6·0	6·8	+0·8	+13
12	5·1	3·7	−1·4	−27
18	9·7	8·3	−1·4	−14
Mean	5·9	5·0	−0·8	−9
(*ii*) *After operation*				
7	1·9	5·0	+3·1	+163
9	3·6	6·5	+2·9	+81
10	1·6	2·8	+1·2	+75
11	3·1	7·9	+4·8	+155
12	4·6	7·0	+2·4	+52
18	3·1	5·8	+2·7	+87
Mean	3·0	5·8	+2·6	+102

A = mean flow during the four minutes preceding the infusion of adrenaline (10 μg. per minute for 10 minutes).
B = mean flow during the last four minutes of the adrenaline infusion.

group was much greater, a mean rise of 97 per cent. Calf blood-flow decreased during the infusion of adrenaline in patients with arthropathy, whereas in the control group a marked increase in flow was recorded, the average rise being 75 per cent. above the initial level.

Resting limb flow and responses to adrenaline after treatment of the primary chest lesion (Tables V and VI; Figs. 4 and 5). Measurements after operation were unfortunately possible in only six patients (Cases 7, 9 to 12, and 18). In each case the studies were made at least two weeks after operation. Resting forearm flow averaged 6·0 ml. before and 3·0 ml. after operation. The corresponding values for calf flow were 5·9 ml. and 3·0 ml. respectively. Successful treatment of the primary chest lesion in patients with arthropathy was therefore associated with a marked reduction in the resting levels of flow in both forearm and calf.

The response to intravenous adrenaline was also modified by effective treatment of the chest lesion. Before operation the infusion of adrenaline caused a slight increase in forearm flow, averaging only 7 per cent., whereas after operation the same dose of adrenaline induced a mean increase in flow of 141 per cent. Mean calf blood-flow decreased (by 9 per cent.) when adrenaline was

given initially, but increased considerably (by 102 per cent.) after operation. After removal of the chest lesion the resting levels of flow and responses to adrenaline were thus very similar to those found in the control group.

Skin temperature during body cooling (Fig. 6). Studies were made in eight patients (Cases 1 to 3, 9, 11 to 13, and 16) initially, and in four of these (Cases 9 and 11 to 13) after operation. A typical response is illustrated in Fig. 6. Before operation the temperature of the skin over the elbow and ankle joints

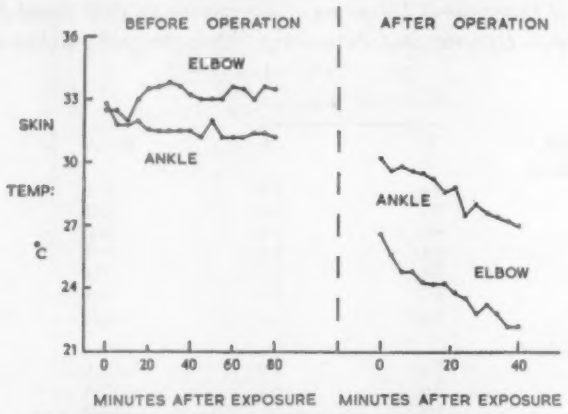

FIG. 6. Skin temperature over affected joints in Case 13 during body cooling, before and after removal of the lung tumour.

was high (32° to 33° C.), and there was only a slight fall in these temperatures during body cooling. After operation the surface temperature at the same points was lower (30° at the ankle and 26° at the elbow), and fell rapidly during the period of exposure. The relief of joint symptoms after operation was thus associated with a reduction in surface temperature over the affected joints.

Femoral arteriography (Plate 34, Fig. 7). The arterial supply to the lower limb in the patient with osteoarthropathy differed from the normal pattern of vascular distribution. Numerous small branches from the main arterial stem were seen running transversely towards the periosteal surface of the long bones, where they gave rise to further vessels. These secondary branches were formed in a characteristic 'T-shaped' manner at the site of indentations in the new periosteal bone, and then ran parallel to, and closely applied to, the surface of the periosteum. Normally the small vessels which emerge from the arterial trunk in the lower limb end in the soft tissues, and branch at acute angles near their termination.

Histological studies (Plates 35 to 37, Figs. 8 to 12). Numerous vessels were noted on the surface of the femur, closely associated with areas of periosteal proliferation. Sections were cut from the specimen of bone after decalcification. Thick-walled arterioles were found immediately beneath the thickened periosteum and overlying areas of new bone formation. Many smaller arterioles were also present in the new bone itself, but not in the old cortex. Similarly,

in the section of tibia, muscular arterioles were found beneath the thickened and inflamed periosteum.

Discussion

In spite of the widespread belief that hypertrophic osteoarthropathy is dependent on some abnormality of the circulation, there has been no general agreement as to the precise nature of this change. Bamberger (1891) first discussed the possibility that peripheral circulatory stasis might influence the growth of bone, and subsequent authors have assumed pulmonary arthropathy to be caused by stasis alone (Compere, Adams, and Compere, 1935; Shaw and Cooper, 1907; Thomas, 1933), or by peripheral stasis and tissue anoxia in the presence of increased vascularity (Branwood, 1949; Mauer, 1947; Means and Brown, 1947). In no instance, however, was adequate evidence provided to support such theories. More recently an increase in peripheral flow has been suggested as the cause of altered bone growth (Mendlowitz, 1954; Semple and McCluskie, 1955; Thompson, 1949). Cardiac output was increased in one dog with experimental arthropathy (Mendlowitz and Leslie, 1942); it was therefore concluded that the production of periosteal lesions depended on a mechanism similar to that presumed responsible for the development of clubbing (Lovell, 1950; Mendlowitz, 1942; Wilson, 1952)—an increased peripheral flow in excess of the nutritional needs of the tissues.

The precise relationship between the development of osteoarthropathy and of clubbing is, however, not known. Though periosteal changes have not been demonstrated in subjects without clubbing of the digits, clubbing is most frequently observed in patients who show no evidence of bone or joint involvement. Nor does the incidence of osteoarthropathy in various diseases necessarily parallel the frequency with which clubbing alone occurs in these conditions. Thus gross clubbing is a common finding in both congenital heart disease and bronchiectasis, whereas osteoarthropathy is rarely associated with the former, and only occasionally with the latter condition. In the majority of recorded cases, as in the present series, pulmonary osteoarthropathy has been secondary to carcinoma of the bronchus; the incidence of clubbing alone in this disease, however, is considered to be less than that observed in bronchiectasis (Wierman, Clagett, and McDonald, 1954). Furthermore, osteoarthropathy is symmetrical in distribution, and does not apparently complicate cases of unilateral clubbing: periosteal changes were not observed in arteriovenous aneurysms of the limbs which were associated with an increased blood-flow and with clubbing (Cohen, Edholm, Howarth, McMichael, and Sharpey-Schafer, 1948; Lewis, 1940; Mendlowitz, 1938; Wilson, 1952). It is therefore possible that changes in the long bones in pulmonary arthropathy are caused by factors additional to those which are believed to determine the production of clubbing alone.

In the present study the mean blood-flow in the hand or foot was similar in patients with osteoarthropathy and in the control group, but the blood-flow

through the forearm or calf was, on average, much greater in the patients than in the control subjects. Since the control group included patients with clubbing of the fingers but no symptomatic or radiological evidence of arthropathy, the increase in mean flow in the forearm and calf cannot be related to the presence of clubbing alone. Consideration of individual results revealed further that there was a wide scatter about the mean in patients with arthropathy, though not in the control subjects. In some instances the resting flow in forearm or calf was more than double the control value (Cases 4 and 11, Table II), while in others the mean flow was within the control range (Cases 3, 5, and 7, Table II). An increased peripheral flow, though frequent, was thus apparently not an invariable finding in pulmonary arthropathy; the periosteal lesions cannot, therefore, be due to an increase in *total* peripheral flow. The intravenous infusion of adrenaline, however, revealed a more consistent abnormality. In the forearm the amount of dilatation was much less than in the control group; in the calf a reduction in mean flow during the infusion of adrenaline contrasted with the marked increase in flow recorded in the control subjects. This abnormal pattern of vascular response was not related to the initial level of blood-flow in the limb, for there was no difference, in the response to adrenaline, between cases in which the resting flow was within the control range (Cases 7 and 14, Table III; Cases 12 and 17, Table IV) and those in which flow in the forearm or calf was initially much greater than normal (Case 11, Table III; Cases 1 and 4, Table IV). The marked and sustained increase in blood-flow in the forearm and calf, normally recorded during an intravenous infusion of adrenaline, is due to a vasodilatation in the vessels of skeletal muscle, which is quantitatively much greater than the simultaneous vasoconstriction occurring in the vessels of the skin (Barcroft and Swan, 1953). Although adrenaline has a constrictor effect on the blood-vessels of bone (Edholm and Howarth, 1953; Ri, 1940), the resting flow through bone is normally considered to represent only a very small fraction of the total flow through the limb (Edholm, Howarth, and McMichael, 1945).

The altered response to adrenaline demonstrated in the limbs of patients with osteoarthropathy can be interpreted in several ways. There might be an abnormality of vascular function in skeletal muscle, impairing the capacity of these vessels to dilate in response to adrenaline; alternatively, the flow might be increased in vessels which are normally constricted by adrenaline, namely, those of skin or bone. There is at present no evidence of any anatomical change in muscle in osteoarthropathy, and the fact that the initial, transient, dilator response to adrenaline was similar in patients and control subjects suggests that there is no general impairment of dilatation in this condition. The possibility of some functional alteration in the circulation through muscle has not, however, been excluded by the present study. Vascular responses in the hands and feet may, to a large extent, be considered indicative of the circulation through skin (Barcroft and Swan, 1953). Since the mean blood-flow in the hand or foot was not above normal in patients with arthropathy, one may infer that there was no great increase in the total flow through the skin. The

altered vascular response demonstrated in this study cannot therefore be attributed solely to an increase in cutaneous blood-flow, and the possibility of an increased flow through bone must also be considered. Skin temperature was high over affected joints and bony prominences, and did not fall when the limbs and trunk were exposed to room air. The femoral arteriogram showed that there was an increased vascular supply to the periosteum; numerous branches from the main arterial stem were seen, running close to the surface of the periosteum and supplying the newly formed bone. Previous histological studies had shown that, though mineralization occurred in periosteal lesions of long standing, the new bone was initially characterized by marked cellular infiltration and by a highly vascular marrow (Gall, Bennett, and Bauer, 1951). In the present study a considerable increase in vascularity was found associated with the areas of active periosteal proliferation. Evidence has therefore now been provided to support previous suggestions of a considerable increase in flow through affected bones (Logan, Marshall, Shepherd, and Whelan, 1954; Mendlowitz, 1941). But whether the blood-supply to bone in osteoarthropathy is so great that it determines all the changes in vascular response is another problem. The direct measurement of blood-flow in human bone is not at present possible, and experimental studies are limited by the problem of producing pulmonary arthropathy in animals (Mendlowitz and Leslie, 1942). Until the condition can be readily and repeatedly produced in laboratory animals, and the flow through skin, muscle, and bone determined separately, the precise partition of flow in the limbs must remain a matter of doubt.

The relation between circulatory changes and symptoms in osteoarthropathy has been the subject of much speculation. In discussing the mechanism by which removal of the lung tumour causes such a striking relief of joint pain and swelling, Semple and McCluskie (1955) stated that the level of peripheral blood-flow fell within two or three hours of operation, but gave no further details. It is difficult to explain the relief of symptoms after operation in terms of decreased peripheral flow alone, for, in a control study of patients without arthropathy, a marked decrease in forearm or calf blood-flow was recorded within 24 hours of a thoracic operation (Ginsburg, 1957). This reduction in limb flow persisted for at least three days, the levels recorded before operation being regained within two weeks. In assessing the relation of a reduction in peripheral flow to the alleviation of joint symptoms, it is therefore important to distinguish changes which occur inevitably after thoracic operations from those which are more directly related to removal of the pulmonary lesion in cases of arthropathy. It is not yet known how far the immediate symptomatic effect of surgery in cases of osteoarthropathy reflects a reduction in blood-flow not specifically associated with removal of the pulmonary lesion, but it is interesting that Semple and McCluskie (1955) have noted the 'remission of symptoms, occurring spontaneously . . . after thoracotomy'. The relief of joint symptoms has also been reported after ligature of the pulmonary artery (Wyburn-Mason, 1948) and after vagotomy (Flavell, 1956), but in the absence of quantitative data the circulatory effects of these procedures cannot be

evaluated. In the present study, however, a *persistent* reduction in peripheral blood-flow was recorded after removal of the pulmonary lesion in patients with arthropathy; two or three weeks after operation, or even later, blood-flow in the calf or forearm was still much lower than before operation. Similarly, the skin temperature over affected joints was much lower after operation, and fell during exposure. Peripheral responses to intravenous adrenaline were also modified by removal of the primary lesion, a marked dilatation being subsequently recorded in both forearm and calf during the infusion of adrenaline. At the time when these measurements were made, however, there was no radiological change in the newly formed periosteal bone. These results may therefore indicate a functional change in the peripheral circulation, associated with removal of the pulmonary lesion, and preceding any anatomical changes such as the resorption of bone.

The relation between an increased blood-supply to the long bones and altered periosteal activity along the shafts, in cases of osteoarthropathy, is not necessarily one of cause and effect. The increased blood-flow may be an associated phenomenon, linked with the formation of new bone, but not of itself responsible for the periosteal changes. It is possible that other factors determine the increase in arterial supply to the long bones and the selective changes in their growth. The nature of such factors is unknown, but it may perhaps be relevant that there is evidence, in cases of pulmonary arthropathy, of anomalies apart from those in bone and joint. Thus bronchopulmonary anastomoses have been demonstrated in the lung vessels of patients with osteoarthropathy, and of patients with clubbing alone (Cudkowicz and Armstrong, 1953; Cudkowicz and Wraith, 1957), though the significance of this finding in the genesis of clubbing remains obscure. The frequent occurrence of endocrine malfunction in patients with pulmonary arthropathy has led to the suggestion that osteoarthropathy may be attributed to altered pituitary activity (Fried, 1943); but other workers have disputed this suggestion (Semple and McCluskie, 1955). The association of gynaecomastia with osteoarthropathy has been known since the time of Bamberger (1891), and in the present series gynaecomastia was noted in four of the 18 men. Of even greater interest was the finding that urinary oestrogen excretion was raised in all three patients in whom it was measured, though only one of these three showed clinical evidence of gynaecomastia. Until the results of studies at present in progress are available, it is not possible to state whether increased oestrogen excretion is an invariable accompaniment of osteoarthropathy, and whether other abnormalities are associated. The above findings, however, raise the possibility that, though changes in bone and joint are the most striking features of this condition, they may be only part of a more general disturbance in bodily function initiated by pulmonary disease.

I should like to thank the many physicians and surgeons who referred patients under their care; Professor H. Barcroft for his advice and criticism; and Miss R. Palmer for technical assistance.

Summary

1. The circulation in the limbs has been measured by venous occlusion plethysmography in 18 patients with hypertrophic pulmonary osteoarthropathy.

2. The resting level of blood-flow in the hand or foot was similar in patients with osteoarthropathy and in a control group.

3. The resting level of blood-flow in the forearm or calf was generally, though not invariably, greater in patients with osteoarthropathy than in the control group. After removal of the primary pulmonary lesion in patients with osteoarthropathy there was a persistent reduction in flow in the forearm and calf.

4. The intravenous infusion of adrenaline in patients with arthropathy increased forearm blood-flow by 36 per cent., but decreased calf blood-flow by 18 per cent.; the corresponding change in the control group was an increase in flow of 97 per cent. and 75 per cent. in forearm and calf respectively. After operation the response in forearm or calf was similar in both groups.

5. Radiological and histological studies showed the presence of numerous vessels closely associated with the newly formed periosteal bone.

6. It is concluded that the blood-supply to the long bones is increased in patients with osteoarthropathy, and that this may, to some extent, be responsible for changes in the peripheral circulation.

7. Other implications of this study are discussed.

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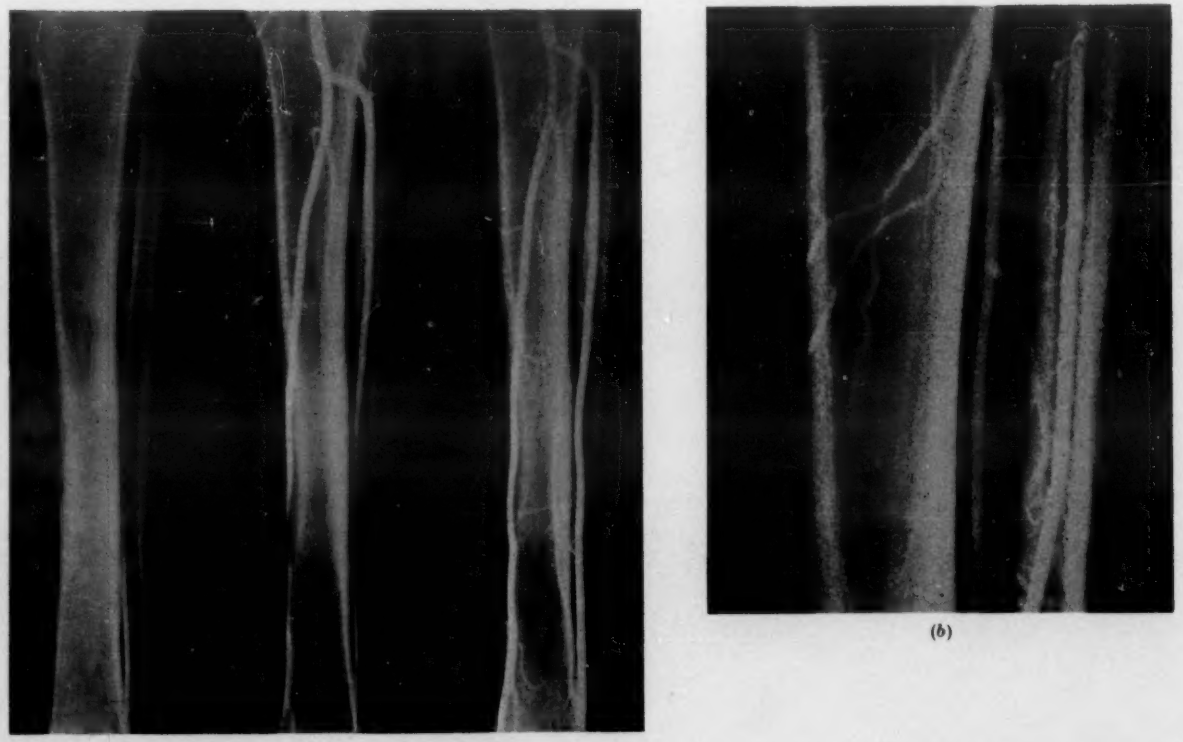

(*a*) (*b*)

FIG. 7. Femoral arteriogram showing the vascular supply below the knee (*a*) in Case 6 and (*b*) in a control subject

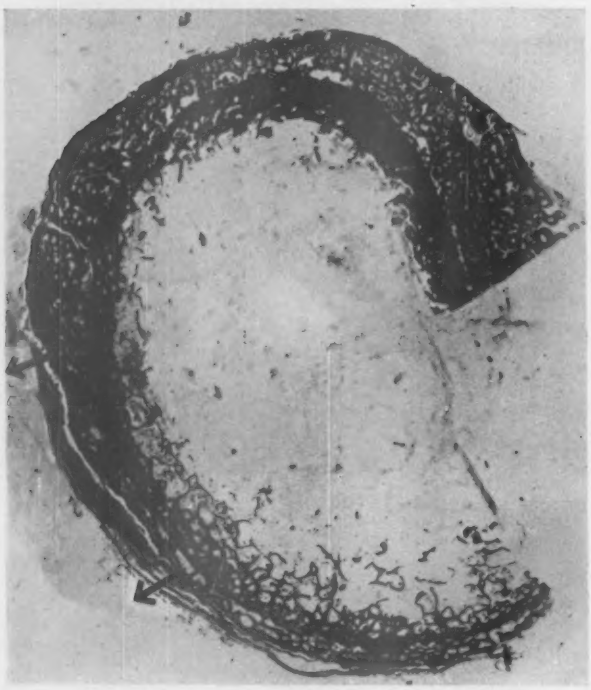

FIG. 8. Case 4. Transverse section of femur, showing thickened periosteum and the area of new bone well demarcated from old cortex

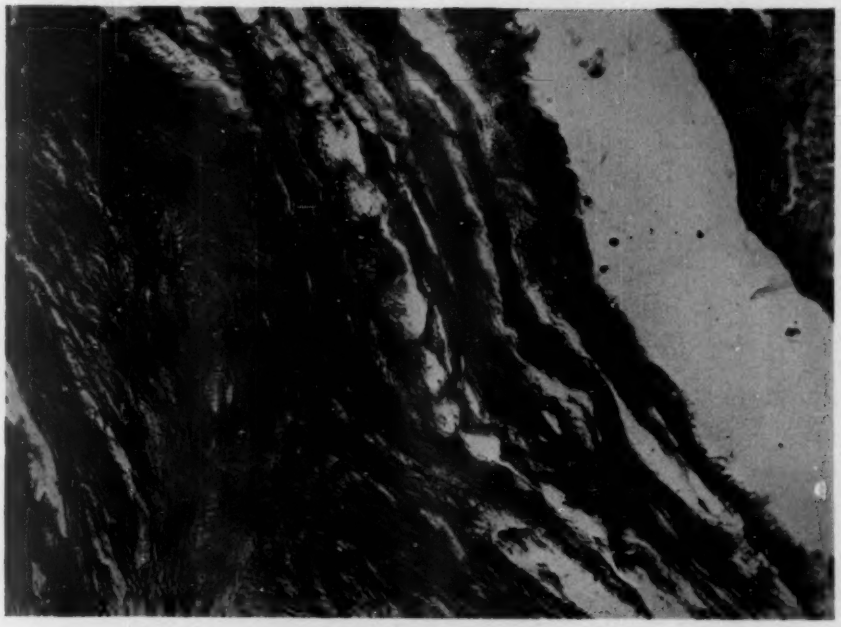

FIG. 9

FIG. 10

FIGS. 9 and 10. Case 4. Photomicrographs (×160) from the area of new bone shown between the arrows in Fig. 8

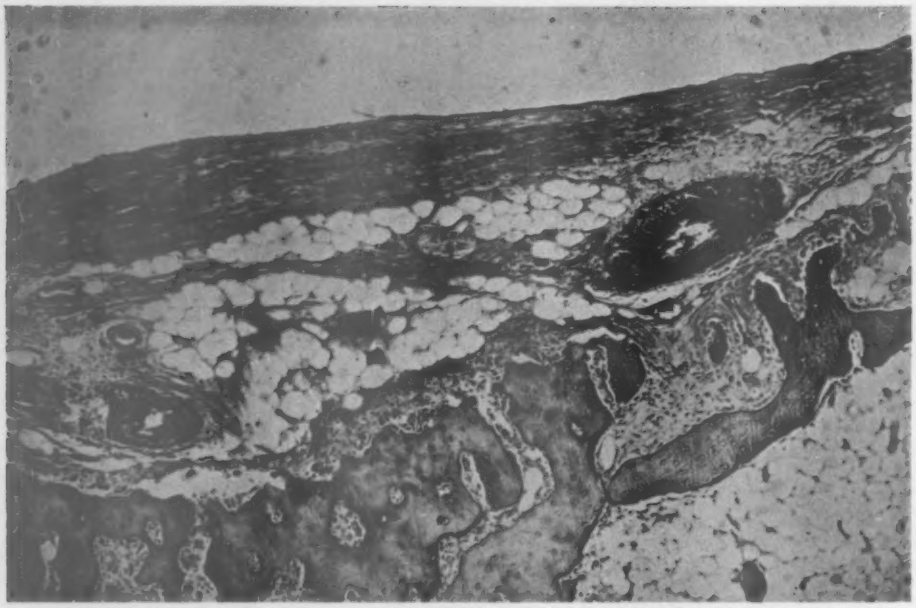

FIG. 11

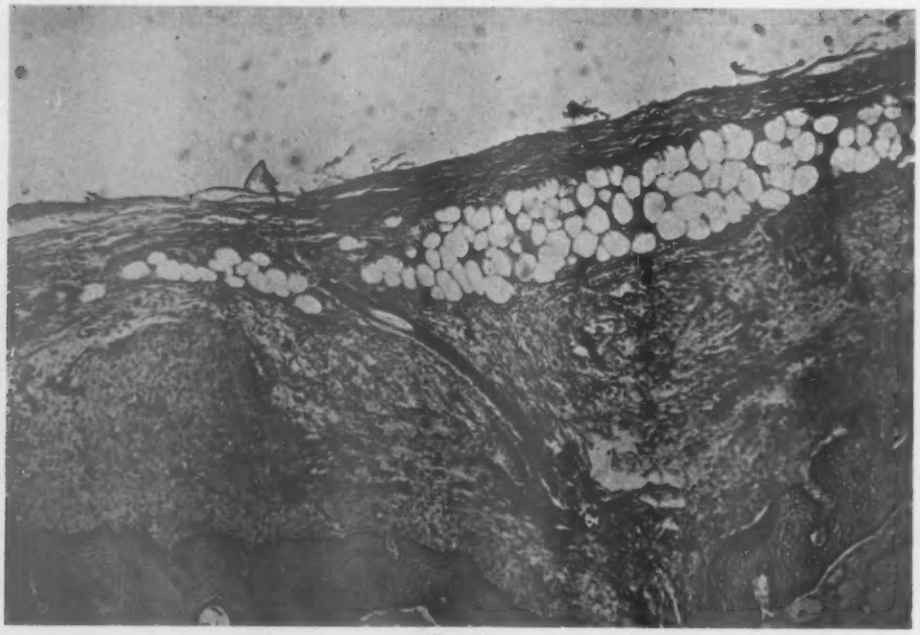

FIG. 12

FIGS. 11 and 12. Photomicrographs ($\times 50$) from a longitudinal section of the tibia in pulmonary osteoarthropathy

616.233–007.64–089.8

THE LONG-TERM RESULTS OF RESECTION FOR BRONCHIECTASIS[1]

By W. H. HELM and V. C. THOMPSON

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The first successful lobectomy for bronchiectasis was carried out by Heidenhain in 1901, and up to 1925 there were reports of 85 further resections (Lisa and Rosenblatt, 1943). In this country the first successful lobectomy was carried out in 1929 by Edwards, who in 1939 reported a series of 168 cases, with an overall mortality of 12 per cent., the mortality for the last 54 lobectomies having fallen to 3·7 per cent. In the early years of the development of resection for bronchiectasis a high risk from operation was justified, since the opinion generally held was that the prognosis without resection was exceedingly grave. Findlay and Graham (1927, 1931) stated that in children with bronchiectasis steady deterioration occurred, leading to a fatal termination. They had observed 32 patients for three to six years, and 12 had died, four after surgery, one from tuberculous meningitis, and the other seven after an average of 2·6 years. Roles and Todd (1933) followed 106 cases for a period of three to six years, and found that 23 of the 49 patients treated medically had died (47 per cent.), and that nine others were totally incapacitated. Cookson and Mason (1938) stated that bronchiectasis was a fatal disease, and that death might occur with alarming rapidity. Perry and King (1940) studied 400 patients with proved bronchiectasis treated at the Massachusetts General Hospital between 1926 and 1938; 260 were treated medically, and included patients unfit for surgery. In January 1939 55 per cent. of these patients were traced and living, 26 per cent. were dead, and 19 per cent. were untraced.

Recently it has become clear that these reports did not represent the prognosis for all patients with bronchiectasis, since they were concerned with patients attending hospital mainly because of the severity of their symptoms. Franklin (1944) observed 24 children for four to 12 years: 15 remained perfectly well, four were delicate, and four were invalids; only one had died. Field (1949) reported a follow-up of 109 children treated medically for three to 10 years, and 10 had died; but nine of these fatalities were early deaths due to the fulminating infection which had caused the bronchiectasis. Brooks (1950) stated that, even in extensively infected cases, the prognosis was less grave than had been thought, and McKim (1952) reported a study of 48 ambulant patients with bronchiectasis, for periods of nine to 20 years (average 12·5 years), and found that only five deaths (10·2 per cent.) were attributable to bronchiectasis. Lander

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(1955) followed up 129 patients from 1935, and only 10 per cent. had died, but 28 were lost sight of during the war. Forty-seven had been followed up for more than 15 years, and five had survived for more than 40 years. Martin and Berridge (1942), Evans and Galinsky (1944), and Fine and Steinhausen (1946) reported the finding of bronchiectasis in service personnel, most of whom were in the highest medical categories and had remained in good health with absent or minor symptoms.

There can be no doubt that the outlook for patients with bronchiectasis has been greatly improved by a better understanding of the condition, by the introduction of postural drainage, and by the use of antibiotics for the acute infective episodes. The outlook with surgery has also greatly improved, and a progressive fall in mortality has been achieved since the early days of resection. Recent reports include those of Chesterman (1951), who recorded a 1·75 per cent. mortality in 120 operations, Mathey and Galey (1952), with a mortality of 3·3 per cent in 120 operations, Jones and Cole (1952), with no deaths in 86 operations, and Ginsberg, Cooley, Olsen, Kirklin, and Clagett (1955), who reported a mortality from operation of 2·7 per cent. and a total mortality of 4 per cent. in 221 resections carried out at the Mayo Clinic between 1942 and 1953. All writers have reported a continued fall in mortality in the later years under investigation. In view of the present low mortality of bronchiectasis, whether treated medically or surgically, it is important to reassess the value of resection in relief of symptoms and in improvement of general health.

Patients Investigated

The object of the present investigations was to establish the long-term effect of resection for bronchiectasis on symptoms and general health, with special reference to patients with generalized bronchitis; and, with the help of bronchograms, to study the effects of the operation and of complications on the remaining segments and bronchi, and to correlate these effects with the symptomatic results. One hundred and fifty-nine patients were treated under the care of one surgeon (V. C. T.) at the London Chest Hospital and the London Hospital from 1939 to 1952. There were 174 resections, 15 patients undergoing bilateral operation. Pneumonectomy was performed in 22 cases. Eighty-four patients were female and 75 male, and the age distribution was as follows:

Years of age . . .	1–10	11–20	21–30	31–40	41–50	50+	*Total*
Number of patients .	25	34	35	32	28	5	159

The operation had been classed as 'palliative' where the disease was too extensive for complete removal, but where it was possible to resect the most severely affected segments, leaving other areas of considerable disease. Generalized bronchitis was assumed to have been present before operation if there was a history of wheezing and tightness of the chest with breathlessness, experienced either persistently or recurrently, with the production of mucopurulent sputum. In every case the diagnosis was confirmed on examination at some period by the presence of generalized rhonchi not entirely cleared by coughing. None of the

patients subjected to resection had radiological or clinical signs of advanced generalized emphysema.

Follow-up after operation. The minimum follow-up period has been two and a half years, and the maximum 16 years, the mean being six years. All the patients were seen at regular intervals after operation, and their condition and symptoms assessed with special reference to general health, weight, the presence of cough and sputum, wheezing, dyspnoea, and the occurrence of acute chest infections. Two patients were lost to observation after three and five years respectively. Serial radiographs have been taken in all patients, and bronchograms carried out one to 15 years after operation in all available adult patients at the London Chest Hospital. The method used was intratracheal intubation with a modified Ryle's tube, designed by one of us (W. H. H.) and made by Messrs. J. G. Franklin and Sons. The opaque medium was a neohydriol sulphonamide mixture.

Grading of results. Patients were classified as 'cured' if they had remained free from symptoms after the period of morbidity immediately following operation. If they were greatly improved, but had slight persistent symptoms, they were classified as 'much improved'; many patients in this group had not entirely lost their cough and sputum, although both were greatly reduced. Others who were convinced that they were better for the operation, and whose histories confirmed this belief, but in whom the improvement fell short of the first two categories, were classified as 'improved'.

TABLE I

Mortality in 174 Resections for Bronchiectasis

	Pneumonectomy (22 operations)	*Lobectomy (137 patients) (152 operations)*	*Total*
Deaths before discharge from hospital .	2 (9%)	1 (<1%)	3 (2%)
Deaths during follow-up period . .	2 (9%)	4 (2·5%)	6 (3·5%)
Total	4 (18%)	5 (3·5%)	9 (5%)

Mortality and complications. There were three deaths in the period immediately following operation and before the discharge of the patient from hospital (Table I). A young man of 19 years, very ill with gross bronchiectasis, amyloid disease, and uraemia, developed a bronchopleural fistula and empyema after right pneumonectomy. A man died with auricular fibrillation seven days after right pneumonectomy, and another died two hours after a lobectomy in a state of shock. There were six later deaths in the follow-up period. Two men developed bronchopleural fistulae and empyemata; one died of a cerebral abscess, and the other of amyloid disease. A woman developed bilateral pulmonary tuberculosis and a tuberculous spine, and died of tuberculous meningitis two years after resection of a bronchiectatic upper lobe associated with hilar calcification. A boy of 11 years developed a bronchopleural fistula after resection of a destroyed infected right lung; soon afterwards he had an abscess in the left lower lobe, and his sputum contained tubercle bacilli. He died two years later of amyloid disease. A man had recurrent attacks of pneumonitis in his left

upper lobe, which became bronchiectatic after left lower-lobe resection, and he ultimately died of a cerebral abscess. A woman died of status asthmaticus two months after left lower lobectomy.

Fourteen patients developed bronchopleural fistulae and empyemata. One had a permanently collapsed left upper lobe after resection of the left lower lobe and lingula, and another developed permanent collapse of the apical segment of the lower lobe after a basal segmental resection. Three others developed progressive fibrosis in the remaining upper lobe after lower-lobe resection.

TABLE II

Long-term Results of Resection in 127 Adults and 32 Children with Bronchiectasis

	Died	*Worse*	*Un-changed*	*Improved*	*Much improved*	*Cured*	*Total*
Radical resection:							
Adults	8	2	11	19	29	49	118
Children	1	..	1	7	5	15	29
Palliative resection:							
Adults	..	..	2	4	2	1	9
Children	..	..	..	2	1	..	3
Total	9	2	14	32	37	65	159

Pathology. In 11 patients there was good evidence that an atelectatic or contracted bronchiectatic lobe was related to a primary tuberculous complex; in 10 there were calcified glands adjacent to the relevant bronchus. One of the latter patients had scattered calcified deposits in the affected lobe, and developed active pulmonary tuberculosis two years after resection; she died of tuberculous meningitis. In another case there was a calcified gland near the middle-lobe bronchus, which was bronchiectatic, and the contracted lobe contained a

TABLE III

Long-term Results of Resection in 22 Adults and 10 Children with Bronchiectasis and Generalized Bronchitis

	Worse	*No better*	*Improved*	*Much improved*	*Cured*
Children	..	..	8	2	..
Adults	2	6	10	4	..
Total	2	6	18	6	..

calcified focus lying in a small cavity. A lobar sequestration was present in three patients: one had a fibroid right lung, with a right basal sequestration and a large artery from the aorta; another had a contracted and bronchiectatic right lower lobe, with a posterior basal sequestration and an abnormal blood-supply; and the third had a contracted and bronchiectatic left lower lobe with a posterior basal cyst, which communicated with the side of the bronchus and was supplied by a large artery coming through the diaphragm. In a fourth patient there was a posterior basal cyst on the right with an abnormal bronchial anatomy; possibly this case represents a similar developmental abnormality. Foreign bodies were found in the bronchi of the resected segments in four cases,

and consisted of a fragment of peanut, a fragment of tomato skin, an inspissated ball of grass seed, and a particle of bone.

Results of Operation

The results in the whole series are summarized in Table II, and those in patients suffering from generalized bronchitis in Table III.

The influence of complications on results. Although the numbers in the respective groups are too small for statistical analysis, it is clear that the group of patients with complications did not do so well as those without. Of 66 patients in whom complications followed operation, 20 (30 per cent.) were classified as symptomatically cured. Ninety-three patients had no complications, and of these 45 (48 per cent.) were classified as cured. The value of even this information is uncertain, since the difference may be partly due to the fact that complications are more likely to occur in patients with the most severe disease and the least favourable outlook.

TABLE IV

Results of Bronchograms in 92 Patients after Resection

Bronchograms carried out on side of resection	100
Bronchograms carried out on contralateral side	46
Number showing new bronchiectasis on side of resection	13
Number showing increase in previous bronchiectasis on side of resection	13
Number showing no increase in previous bronchiectasis on side of resection	10
Number showing new bronchiectasis on contralateral side	3
Number showing increase in previous bronchiectasis on contralateral side	4
Number showing no increase in previous bronchiectasis on contralateral side	11

Bronchograms on the side of resection were completed in 100 cases at intervals of from one to 15 years after the operation, the mean period being five years (Table IV); in 64 of these patients there was no bronchiectasis, and in 10 patients previous residual bronchiectasis had not increased since the operation; thus in 74 per cent. there was no deterioration. In 13 there was new bronchiectasis on the side of resection, and in another 13 previous bronchiectasis had increased; thus in 26 per cent. there was deterioration. In 46 patients bronchograms were also obtained on the side which had not been submitted to resection; there is some selection in this group, since bilateral bronchograms were usually not considered justifiable in a symptom-free patient. In 28 of these 46 patients (61 per cent.) there was no bronchiectasis on this side, and in 11 previous bronchiectasis had not increased; thus 39 out of 46 (85 per cent.) showed no deterioration. In three there was new bronchiectasis on this side, and in four previous disease had increased. Thus there was deterioration in the contralateral lung in seven out of 46 cases (15 per cent.), as compared with 26 per cent. on the side of resection.

The influence of complications on the bronchographic appearances is shown in Table V. Deterioration was observed in 13 (32 per cent.) of 41 cases in which resection had been followed by complications, and in 13 (22 per cent.) of 59 cases without such complications.

The influence of generalized bronchitis. Of 100 bronchograms performed on the side of resection, 25 were in bronchitic patients, and 12 of these (48 per cent.) showed deterioration. Seventy-five were in patients without bronchitis, and of these only 14 (19 per cent.) showed deterioration.

Preservation of the apex of the lower lobe. Twelve basal segmental resections were carried out with preservation of normal apical segments of the lower lobe. One of these operations was followed by permanent collapse of the apical segment, which became bronchiectatic. In seven other patients bronchograms were completed and were normal.

TABLE V

The Influence of Complications following Operation on the Bronchographic Appearances

Complications	*No change*	*Slight deterioration*	*Moderate deterioration*	*Gross deterioration*
Empyema and fistula	6	2	1	..
Empyema without fistula	3	..	..	..
Parabronchial 'pocket' empyema	2	..	..	..
Lobar collapse, more than 1 day but not permanent	17	2	2	1
Permanent lobar collapse	..	..	..	2
Pulmonary tuberculosis	..	1	..	..
Progressive fibrosis in remaining remaining lobe	..	..	1	1
None	46	4	4	5

TABLE VI

Relationship between Symptomatic Results and Bronchographic Appearances after 100 Resections in 92 Patients

	Number of patients					
Bronchogram	*Died*	*Worse*	*No better*	*improved*	*Much improved*	*Cured*
No change	..	..	6	8	16	37
Slight deterioration	..	..	2	4	..	2
Moderate deterioration	..	1	3	2	2	..
Gross deterioration	1	1	3	2	2	..

The relationship of symptomatic results to bronchographic appearances is shown in Table VI. Thirty-seven out of 67 patients (55 per cent.) with no deterioration in the bronchographic appearances were cured, whereas only two out of 25 (8 per cent.) with such deterioration were cured, and both of these patients had only slight bronchial changes. On the other hand, four patients (44 per cent.) with gross deterioration and four (50 per cent.) with moderate deterioration were symptomatically improved or much improved. Six patients (43 per cent.) who were symtomatically no better showed no deterioration in the bronchographic appearances.

Details of patients who were no better for operation. Sixteen patients were not improved by operation. One was a child of five years; the other 15 were adults. Eight of the adults had generalized bronchitis before operation, and none of these eight patients had complications after operation, apart from

transitory lobar collapse in two cases. In each of these bronchitic patients there was temporary improvement after operation, but the symptoms of bronchitis gradually returned to the previous level, and in two instances became more severe. Bronchograms after operation were obtained in four of these patients, and showed new bronchiectasis in two. In both instances this had occurred in the left upper lobe, after resection of the left lower lobe and lingula, which had occupied considerable space. The bronchi became generally dilated, and showed gross bronchitic changes. One of these patients maintained her improvement for six years after operation, but then the recurrent attacks of bronchitis became more severe, and she developed signs of cor pulmonale with early heart failure. For the last two years she has been treated with continued oxytetracycline (terramycin), with great improvement.

Eight patients who did not have bronchitis were no better for their operations. A man aged 24 underwent palliative resection of the right lower and middle lobes; he developed a bronchopleural fistula and empyema, which required drainage, and the fistula ultimately closed after two years. His cough, sputum, and general condition have remained unchanged; bronchograms eight years after operation showed no bronchiectasis on the side of resection, but there was an increase in the previous bronchiectasis of the left upper lobe and lingula. A woman aged 33, whose symptoms were slight, and consisted of persistent cough and sputum since whooping-cough at the age of three years, had a left lower lobectomy, without complications. After operation her general condition remained good, but her symptoms were little changed, and bronchograms eight years later showed new slight bronchiectasis of the lingula, and possibly also of the right upper lobe. A man aged 44 had resection of the left lower lobe and lingula; operation was followed by partial collapse of the left upper lobe for several weeks, possibly due to a small fistula; the lobe ultimately expanded to fill the space, but remained small, and serial X-rays showed changes consistent with progressive fibrosis throughout the lobe; bronchograms five years after operation showed generalized dilatation, with beading and diverticuli. The patient was improved after his operation, but six years after it he developed a cerebral abscess, which required aspiration. He is now awaiting resection of the left upper lobe. A woman aged 27 had resection of the left lower lobe and lingula, followed by a right basal segmental resection. There were no complications from the first operation, but the second was followed by a bronchopleural fistula and empyema; the fistula was ultimately closed by a skin-flap operation. She was not apparently subject to generalized bronchitis before operation, but in recent years she has had recurrent attacks of acute bronchitis, with increasing cough, sputum, and breathlessness in the intervals between the acute episodes. Serial chest X-rays suggest increasing fibrotic changes in both lungs, and bronchograms seven years after the last resection show considerable irregularity of the bronchial lining, with beading of some branches, but only slight patchy dilatation. A man aged 33 had resection of the right lower and middle lobe; there were no immediate complications, but serial X-rays suggested progressive fibrosis in the right upper lobe compatible with pulmonary tuberculosis;

examination of the sputum, however, gave persistently negative results, and bronchograms four years after operation showed distortion and irregular dilatation of the bronchi of the right upper lobe; his original symptoms of cough and sputum remained unchanged. A woman aged 21 underwent palliative resection of the lingula and middle lobe, leaving slight bronchiectasis in both lower lobes; there were no complications, but her cough and sputum remained unchanged; bronchograms five years after operation showed no definite change, but one segment of the lingula remained, and the bronchial dilatation had increased. A man aged 34 had resection of the left lower lobe and lingula; the operation was followed by a bronchopleural fistula and empyema, necessitating drainage and a skin-flap operation. Later he had an acute pneumonic infection in the right lower lobe, and empyema; bronchograms have not yet been carried out. A girl aged five years underwent resection of the left lower lobe and lingula, followed by recurrent and ultimately permanent collapse of the left upper lobe, which became bronchiectatic, and her cough and sputum persisted. She has recently undergone left upper lobectomy, with great improvement. Thus 14 of the 16 patients who were not improved had either generalized bronchitis or serious complications after operation. The other two developed new or increased bronchiectasis.

Discussion

Results of resection. Forty-one per cent. (65) of the total of 159 patients were cured, 23 per cent. (37) were 'much improved', and 20 per cent. (32) were 'improved'; 64 per cent. (102), therefore, were cured or 'much improved', and 84 per cent. (134) were better for the operation; nine per cent. (14) were unchanged, and one per cent. (two) were ultimately worse. Six per cent. (nine) died in hospital after the operation or during the follow-up period. It is very difficult to compare these results in detail with any series of medically treated patients, since the early reports dealt largely with ill patients in hospital before the introduction of chemotherapy and modern physiotherapy. The more recently published medical series contain many examples of patients unfit for surgery because of the distribution of the disease or their general condition. In the present series, 47 per cent. (15) of 32 children were cured. Field (1949) found that 54 per cent. of 93 children treated surgically were cured, whereas only 12 per cent. of 109 treated medically for three to 10 years lost their symptoms; on the other hand, only three children treated medically were worse. McKim (1952), in a study of 49 ambulant patients with bronchiectasis in a Chest Clinic over a period of nine to 20 years, found that 53 per cent. (26) had less sputum than when first seen; 24·5 per cent. (12) had the same quantity of sputum, and only 6·1 per cent. (three) had more; 10·2 per cent. (five) had died of conditions attributable to bronchiectasis.

It is misleading to attempt to assess the results of surgical treatment from the point of view of cure alone, since the highest percentage of cures will be among

patients with slight disease and mild symptoms, whereas the greatest benefit may be obtained by more severely disabled patients, who do not become entirely free of symptoms. In the present series 12 patients underwent palliative resection of the most severely affected areas, leaving significant bronchiectasis elsewhere; only one patient in this group became entirely free from symptoms, but three were much improved and six were improved, leaving two whose condition was unchanged. Thus 10 (83 per cent.) were better for their operation, and the improvement was often considerable.

The chance of a complete symptomatic cure following surgical resection depends on whether symptoms arise entirely from the bronchiectatic area, and whether the disease is well localized and capable of complete excision. Symptoms such as haemoptysis and pain may arise from well-localized disease in the absence of severe prolonged infection, and cure usually follows removal of the affected area. In the presence of prolonged severe infection, however, although the bronchial dilatation may be well localized and completely removed, the patient's cough and sputum, although reduced, may persist. This may be due to persistent antral infection, but is probably often due to a local spread of infection from the bronchiectatic area before operation. Careful inspection of bronchograms taken before operation in some of these patients suggests that neighbouring bronchi, although not dilated, were not entirely normal, and in some instances they became progressively diseased and dilated after resection.

In the great majority of our patients who were symptomatically better for their operation there was also a marked improvement in general health; they put on weight, felt more energetic, and tired less easily, and colds ceased to affect their chests to the same extent as previously. This general improvement was often pronounced in children, and of a greater degree than could have been expected from the onset of puberty alone.

Bronchitis. All the patients with bronchitis and bronchiectasis were temporarily improved after resection, with less cough, sputum, and wheezing, and better general health, but none entirely lost their predisposition to recurrent bronchitis, which often followed upper respiratory infections. All the 10 children maintained their improvement, but in six (27 per cent.) of the 22 adults the attacks of bronchitis gradually increased, with a return of cough, sputum, and other symptoms to the former level, and in two others (9 per cent.) further deterioration ultimately took place. Fourteen (64 per cent.), however, had maintained their improvement to the end of the follow-up period. Bronchograms on the side of resection were performed in 21 bronchitic adults and four bronchitic children: 12 (48 per cent.) showed deterioration, but there appeared to be no close correlation between the bronchographic appearances and the symptomatic results in this group. In the patients who were improved symptomatically 10 bronchograms showed deterioration, whereas 11 did not, and in the patients who were no better or worse two bronchograms showed deterioration and two did not. It is difficult to believe that the development of considerable new or increased bronchial dilatation will not ultimately be followed by symptomatic deterioration in most patients.

There is no doubt that resection of bronchiectatic areas in bronchitic patients gives less satisfactory results than in those without bronchitis, and that further bronchial dilatation is more likely to occur. This is probably especially true if the resected parts were occupying considerable space. This combination of diseases is, however, usually severely disabling and progressive, and it is doubtful whether better results would be obtained by the accepted medical measures. Possibly the addition of long-term antibiotic therapy at the time of and after the operation would, by suppressing or eliminating the general infection, reduce the danger of further dilatation of the already weakened bronchi when subjected to the additional strain of the anatomical and mechanical changes following operation. This additional treatment seems especially indicated where it is necessary to preserve branches which bronchograms before operation show to be already dilated or otherwise abnormal. None of our patients had radiological or clinical signs of advanced generalized emphysema, which would usually contra-indicate resection of bronchiectatic segments. Where the bronchiectasis and infection are severe, however, and the affected segments occupy little space, a moderate degree of generalized emphysema need not contra-indicate resection.

Preservation of the apex of the lower lobe. In order to limit resection as far as possible, basal segmental resections are often performed, with preservation of the normal apices of the lower lobes. Some writers have, however, reported unfavourable results from this operation. Kergin (1950) had only five good results in 11 patients and, when the other six resections were followed by serious complications, and four of these patients later developed bronchiectasis in the preserved segment, he abandoned the method. In the present series 12 basal segmental resections were performed; atelectasis of the apical segments occurred in two patients, and was permanent in one. Bronchograms were carried out after operation in eight patients, and were normal in seven, but new bronchiectasis developed in the permanently collapsed segment, which was later resected. Hoffman (1955) reported his results in 51 patients, and found that bronchograms taken soon after operation showed some degree of atelectasis or bronchial dilatation in the preserved segments in 24 cases, but later films and bronchograms showed that in 18 of these patients re-aeration had taken place and the clinical result was good. The atelectasis persisted in four, but he believed that re-aeration may take place between one and six years after operation, and therefore recommended conservative treatment of this complication, where possible, for several years. Collis (1953) reviewed the findings after operation in 233 cases of bronchiectasis treated by resection; follow-up bronchograms were carried out after 178 operations. After 74 basal segmental resections he found that new bronchiectasis had developed in the preserved apical segment in five cases, but that this disadvantage was largely balanced by a lower rate of deterioration in the upper lobe in these patients than in those who had undergone total lower lobectomy. We agree with his conclusion that the slightly higher risk of new bronchiectasis occurring, if the apex of the lower lobe is retained, is a small price to pay for the preservation of the function and volume of this segment.

Complications. Permanent lobar collapse and progressive fibrosis of the remaining lobe occurred in five of our patients after lobectomy; in each case moderate or gross bronchiectasis developed, and only one of these patients was improved symptomatically. Temporary lobar collapse occurred in 38 patients, but 34 (89 per cent.) were improved symptomatically by the operation, and deterioration in the bronchographic appearances had occurred in only five (23 per cent.) of the 22 patients investigated. This percentage is almost the same as that found in patients without complications. Fourteen patients developed bronchopleural fistulae and empyemata; four died, and three were symptomatically no better for operation. Bronchograms were completed in nine of the 10 survivors in this group, and deterioration had occurred in only three. It appears that the bad results following this serious complication are due more to the direct effects of the fistulae and infection than to the occurrence of new bronchiectasis, and, providing such effects are successfully treated, a good result may be obtained. The early patients in the present series were operated on before the advent of antibiotic therapy, and it is in this group that many of the more serious complications occurred. Modern surgery, with the extensive antibiotic cover which is available, is considerably safer, and complications due to infection and fistulae are now extremely rare. It must be admitted, however, that resistant strains of staphylococci present a serious problem in antibiotic cover at the present time.

Bronchograms. A high standard of bronchography is essential for the proper assessment of a case of bronchiectasis, and great care is needed in the interpretation. This is especially true in children, in whom the appearances of the bronchograms obtained under general anaesthesia often vary considerably if repeated after a short interval. This is, no doubt, sometimes due to transient atelectasis, but on other occasions to variation of the intrabronchial pressure during anaesthesia, and to the radiograph being taken during different stages of respiration. Variation in the quantity and quality of the opaque medium, and the presence of secretions in the bronchial tree, may also produce misleading appearances. It is important to look carefully for abnormalities other than bronchial dilatation: Simon and Galbraith (1953) described the characteristic bronchographic appearances in bronchitis, and found beading, diverticuli, diminished branching, and peripheral pooling in most cases, and Reid (1955) has described the pathological changes associated with these appearances. Most of our bronchitic patients showed these changes, and we have seen similar beading and diverticuli in patients without the signs and symptoms of generalized bronchitis; this has almost always occurred in branches close to the bronchiectatic area, and probably indicates the presence of infection. These changes, whether widespread as in generalized bronchitis or localized and due to a spread of infection from the established bronchiectasis, suggest that increased disease and dilatation may follow resection if these already weakened areas are preserved and take part in the compensatory distension.

Bronchograms after operation are of considerable interest in every case, and are essential for full assessment, especially where symptoms have persisted. In

the present series 100 bronchograms after operation were carried out on the side of resection; in 23 instances some bronchiectasis had been left on this side at operation; three of these instances were due to a mistake at operation, and in each case only one segment of a diseased lingula had been removed, and the later bronchograms showed increased disease in the remaining segment; in one of these cases there was, in addition, new bronchiectasis in the anterior and posterior segments of the left upper lobe. In the other 20 cases some bronchiectasis, mostly of slight degree, was intentionally left behind at operation, and later bronchograms showed increased dilatation in 10 cases; six of these patients also had generalized bronchitis, and bronchograms taken before operation in three had shown bronchitic changes. New bronchiectasis was seen on the side of resection in 13 cases; in eight it was associated with, and probably due to, serious complications after operation, and three of these patients also had generalized bronchitis; three of the other five had bronchitis, and in two of these bronchography before operation showed slight bronchitic changes. The other two developed slight terminal dilatation in the bronchi of the anterior segment of the left upper lobe, after resection of the left lower lobe and lingula; they had no complications after operation, and no bronchitis or evidence of localized infection before operation.

Bronchograms of the lung not submitted to resection were carried out after operation in 46 patients. Bronchograms on this side before operation had shown some degree of bronchiectasis in 15; in four of these patients the bronchiectasis had increased, and in 11 it remained unchanged. In one patient, six years after resection of the left lower lobe and lingula, new bronchiectasis had developed in the lateral branch of the anterior bronchus of the right upper lobe; this patient had recurrent bronchitis, and after resection developed gross bronchiectasis in the left upper lobe, with increasing sputum and breathlessness. In the intervals between attacks of bronchitis the signs consisted of crepitations localized to the left side of the chest, which, with the deterioration shown in the bronchogram on this side and the persistent purulent sputum, suggested severe and persistent infection in the left upper lobe. It seems probable, therefore, that the bronchiectasis on the right side was due to a spill-over infection, resulting from the repeated aspiration of infected bronchial emboli during sleep in the lateral posture, gradually overcoming the protection of cough and ciliary action. There had been no evidence of any acute pneumonic episode in this newly affected area. In one other patient it is possible that a somewhat similar mechanism resulted in new bronchiectasis in the same area. In this instance, however, the bronchograms before operation were not of a sufficiently high quality to make it certain that the right upper lobe had been normal. This patient had resection of the left lower lobe and lingula in 1947, and remained free of symptoms, apart from chronic nasal sinusitis, for three years; her cough, sputum, and slight general malaise then returned, and bronchograms showed the left side to have remained clear of disease, but considerable dilatation of the anterior bronchus of the right upper lobe; after resection of this segment the patient again became free of symptoms. In view of the absence of disease elsewhere, it is possible that the

nasal sinuses were the source of infected bronchial emboli, leading to new bronchiectasis. In one other patient there was probably slight new bronchiectasis in the lower lobe of the side opposite the resection.

Although the results of bronchograms on the two sides are not strictly comparable, it seems certain that the higher rate both of deterioration in previous disease and of development of new bronchiectasis on the side of operation is due largely to complications and to the mechanical changes following resection, and is probably sometimes due to the effect of these factors acting on a bronchus previously weakened by a local spread of infection or by generalized bronchitis.

Respiratory function after operation. No respiratory function tests have been carried out in the present series, but, apart from a few of the patients who had generalized bronchitis before operation, only one patient has complained of increased dyspnoea on exertion. This man developed generalized bronchitis after a resection attended by complications, and subsequent bronchograms showed advanced bronchitic changes, with only slight patchy dilatation. Some patients, including a few with bronchitis, are convinced that they are less breathless than before operation, and this sometimes seems to be due to the fact that previously exercise would cause coughing, and thereby breathlessness, whereas after operation cough and sputum were eliminated or greatly reduced.

Long, Norris, Burnett, and Wester (1950) reported the results of bronchospirometry before and after lobectomy for bronchiectasis. They found that the operation did not change the overall ventilation to any extent, and often there was an increase in the maximum breathing capacity. In 18 out of 24 cases operation was followed by some loss of function on the diseased side, but this loss was balanced by increased function of the opposite lung. They found that there was an association between complications of operation and reduction of oxygen absorption on the side of resection, but that after resection, even without complications, there was a reduction in the total air moved on this side. Smith, Siebens, and Storey (1954), in a study of the cardio-respiratory function of 40 patients before and after resection for bronchiectasis, confirmed the view that there was loss of function on the side of resection after thoracotomy, even when little or no pulmonary tissue was resected, and that complications after operation increased this loss. The above-mentioned tests were carried out early in the follow-up period, and in order to establish the long-term effect of resection on lung function it would be necessary to repeat the tests at intervals, and to compare the results with those obtained in a parallel series of patients who had not undergone operation. It is encouraging that Long, Norris, Burnett, and Wester (1950) found that there was increased function in the disease-free lung after resection on the other side. This result is possibly due to decreased cough and sputum, and to elimination of the reservoir of infection. In the long run this may be of great importance to the preservation of total lung function, and may outweigh the disadvantage of the decrease in ventilation on the side of resection.

Conclusions

Although great improvement usually follows when efficient medical measures are instituted for bronchiectasis, this treatment has to be continued indefinitely, and the improvement cannot be expected to be equal to that obtained by total removal of the diseased segments. Resection, therefore, remains the ideal treatment for bronchiectasis. In many patients, however, the outlook with resection is uncertain, since if the diseased segments occupy considerable space, and especially if there is any spread of infection to neighbouring segments, or co-existing generalized bronchitis, deterioration may ultimately follow in the remaining segments. This possibility is not necessarily a contra-indication to operation, since the patient may remain greatly improved symptomatically even if new bronchiectasis develops.

Patients with associated generalized bronchitis are usually improved for a time by resection of bronchiectatic segments, but in many the symptoms gradually return to the previous level, and further deterioration may occur. Resection in this group should probably be confined to patients in whom the bronchiectatic segments occupy little space. Long-term antibiotic therapy should be given before and after operation. Severe long-standing bronchitis or advanced generalized emphysema contra-indicate resection, not only because of the risk, but because little is likely to be gained by operation at this stage.

When new bronchiectasis develops after operation it is usually in segments adjacent to those resected, and it is rare to find such new development in distant segments, especially of the other lung.

There is seldom, if ever, any urgency for operation in bronchiectasis, and in children especially careful assessment should be made. Providing medical measures are thoroughly carried out, no harm is likely to occur by waiting, and it is often possible to delay bronchograms until they can be carried out under local anaesthesia, which is much safer and gives more reliable results than general anaesthesia.

For full assessment of the results of surgery in bronchiectasis, a prolonged follow-up, with bronchography, is essential.

We are indebted to the many Registrars at the London Chest Hospital who helped with the early work in this series, and to Drs. L. M. Reid and J. Dawson for their helpful criticism.

Summary

The results of surgery in treatment of bronchiectasis in 159 patients are reviewed, with special reference to the presence of generalized bronchitis, the influence of complications after operation, and the subsequent development of new or increased bronchiectasis.

Eighty-four per cent. of patients (134) were improved by operation, nine per cent. (14) were unchanged, and one per cent. (two) ultimately became symptomatically worse than before operation. Six per cent. (nine) died before discharge from hospital, or in the follow-up period.

Most patients with coexistent bronchitis and bronchiectasis were considerably improved for a time by operation, although the symptoms of bronchitis usually persisted to some extent. Symptomatic deterioration and the development of new or increased bronchiectasis occurred more frequently after operation in this group than in patients without bronchitis.

Complications after operation, other than permanent lobar collapse or progressive fibrosis, do not appear frequently to have been the cause of new or increased bronchiectasis.

It is concluded that surgical resection remains the treatment of choice for bronchiectasis in carefully selected patients.

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OSTEOMYELITIS VARIOLOSA[1]

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With Plates 38 to 40

In the early months of 1957, in the town of Ibadan in south-west Nigeria, there occurred an epidemic of smallpox which was part of a more widespread outbreak in that country. In the course of this epidemic we observed at the University College Hospital many examples among children of a skeletal complication, which usually came to notice as an arthritis of the elbows; such a complication has frequently been recorded, but in widely diverse and often inaccessible journals. The only account of the condition that we can trace in British medical literature was written as long ago as 1887. In the present communication we have used our own experience of 15 cases of this bone and joint lesion, and have drawn upon the writings of previous workers, in order to provide a comprehensive account of it as a clinical entity and to outline our views upon its pathogenesis.

Historical Review

The first published reference that we have traced is a paper in 1873 by Bidder, who described five cases of purulent arthritis during a smallpox epidemic in Germany. Two years later Kolaczek (1875), from Breslau, recorded a 21-year-old boy with osteomyelitis of a clavicle and both radii, which had followed smallpox after an interval of 18 months. Kolaczek was intrigued by the symmetry of the elbow lesions, and supposed a direct relationship to the smallpox infection. Neve, in 1887, provided the first and only mention in British literature of 'Bone Disease after Smallpox', of which he reported four cases in children seen in Kashmir. Two of these children suffered from osteomyelitis, without joint involvement, of the ulna and scapula respectively. One had arthritis of several joints, including the elbows, and a fourth arthritis of the shoulder. In each the disorder closely followed smallpox. Neve employed drastic methods of treatment, such as excision of joints, but remarked that the prognosis is good if the patient is not undernourished, and dwelt upon an association between malnutrition and involvement of bones. He stated that such involvement was so common locally that the native hakims practised bleeding of patients in the later stages of smallpox in order to avert it.

In 1903 Debeyre, writing from Lille, complained that, although post-variolar

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osteomyelitis was recognized clinically, there was no publication on the subject to attract attention. He then described a case of low-grade non-suppurative osteomyelitis of the humerus, arising on the fourth day of smallpox, in a 20-year-old girl. Although there was a little restriction of elbow movement, the condition principally involved the bone. Citing case reports of Mauclaire (1895) and Voituriez (1903), he concluded that the bone complications of smallpox are divisible into a rarer destructive purulent osteitis and a milder and more frequent non-suppurative inflammation of bone, exemplified by his patient. In the same year Ingelrans and Taconnet (1903), also from Lille, published three cases of osteomyelitis after smallpox. Although in one there was a fulminating lesion with septicaemia, the two others pursued a subacute course with early and quiet onset.

Two important papers were written in 1910 and 1913 from the Philippine Islands by Musgrave and Sison. They described 18 cases, and the common feature was a shortening of the shafts of certain bones, especially those of the upper extremity. There was frequently also irregularity in the shape of the joints, as well as a variable amount of loss of movement or even ankylosis. Although their patients were adult, all had had smallpox in childhood, usually when very young, and in no instance at a later age than 14 years. This affection of bone was a complication locally dreaded. In every case but one the elbow was involved, and sometimes other regions. The authors could not explain the special susceptibility of the upper limb, but correctly inferred from physical signs and X-rays that the deformities were caused by partial or complete destruction of the secondary epiphyseal centre of ossification, with consequent arrest of growth. One of their patients, with a deformed elbow, died from intercurrent disease, but at autopsy the only findings, besides shortening of the diaphyses of radius, ulna, and humerus, were alterations in the size and outline of the contiguous ends of the bones. In this instance the articular cartilage of the elbow-joint was partially destroyed, suggesting to Musgrave and Sison an inflammatory rather than a metabolic origin for the lesion. To support their belief that smallpox was responsible for the lesion, they quoted Osler and McCrae's textbook (1907), which states that 'arthritis may occur in smallpox, usually in the period of desquamation, and may pass on to suppuration'. Similar late deformities of the limbs after smallpox have been described by Cange (1912), Brown and Brown (1923), Sheldon (1923), Cathcart (1924), Lombard (1929), Eikenbary and LeCocq (1931), Cossu (1936), and Maranich (1951). Sircar in 1912 reported a case of necrosis of bone in smallpox, the earliest reference to this disorder to come from China. Schwenk (1912) described a 14-year-old girl who had developed arthritis of both shoulders soon after smallpox seven years before. Sequestra formed in the scapula and were removed, and ultimate function of both shoulders was perfect. Schwenk commented upon the rarity of symmetrical osteomyelitis except after typhoid and smallpox, and recommended in all such cases an inquiry about these illnesses and the performance of a Widal test.

In 1923 Brown and Brown, writing from Texas, first clinically employed the

term 'osteomyelitis variolosa' (which was coined by Chiari in 1893 to describe his findings in the bone-marrow of smallpox patients) in the title of their valuable paper, thereby designating the process from which their two patients, with late deformities after smallpox in childhood, had suffered. One was six years old at the time of observation, and had had smallpox only three years previously, but shortening was already evident in a number of her bones. Because neither patient had scars or sinuses, the authors believed that the lesion had not been a suppurative one. They said that bone complications of smallpox were rare, but might be of two types. The first was an ordinary pyogenic, metastatic osteomyelitis, such as might occur with any acute infectious disease. The second type, to which they gave the name osteomyelitis variolosa, was a necrotic, non-suppurative osteomyelitis, probably due to the smallpox virus, which usually involved the diaphyseal ends of long bones, destroying the epiphyseal lines, and causing late deformities by destruction or premature fusion of epiphyses. Sterile pus, which is sometimes found within smallpox vesicles, derives from an analogous aseptic inflammation in bone. Brown and Brown asserted that this second type most commonly affects children, and often passes unrecognized during the acute stage. They were the first to state definitely that a viral osteomyelitis is responsible for this complication of smallpox. Moreover, they realized the peculiarly specific nature of the lesion, observing that a similar process principally affecting epiphyses is seen only in osteochondritis juvenilis.

Huenekens and Rigler (1926) published from Minneapolis the first account of a case of osteomyelitis variolosa in the acute stage. During the early days of an attack of smallpox in a four-year-old girl, symmetrical inflammation of certain joints of the arms and legs became evident, with X-ray evidence of destructive osteitis at the epiphyseal lines of contiguous bones. A slight sustained fever and a leucocytosis up to 22,000 per cu. mm. were manifest for many weeks. Function gradually returned to the joints during 11 months of subsequent observation; irregularity of growth persisted in some affected bones and, furthermore, the appearance of some epiphyses was delayed. The authors made X-ray studies of the bones of a large number of other smallpox patients, but found no abnormality even in patients with severe bone pains.

By 1931, when Eikenbary and LeCocq from Seattle reported three examples of late deformity after smallpox, knowledge of the lesion had become general enough for them to recommend that a past history of smallpox should be inquired after whenever obscure deformities of the extremities, with inequality in length, were seen. The exact symmetry of radiographic bone lesions, in an 18-year-old Annamite girl with swellings around elbows and knees after smallpox, attracted the special comment of Long, Nguyen Khac-Can, and Nguyen Phan (1938); this case is also noteworthy as having occurred in an older patient. Navasimhan (1940) reported 16 cases of bone and joint disorder in smallpox which he had seen in Madras. Twelve of these instances were deformities observed a long time after the disease. Navasimhan embraced the distinction made by Brown and Brown (1923) between pyogenic and virus types of

inflammation, but he allocated his cases to one or other category without supporting evidence or discussion. He also complicated the main groups by further subdivision, and appeared to accept epiphyseal destruction as a regular feature of pyogenic arthritis. Fan (1940), writing from China, contributed an account of two unvaccinated children with smallpox, in whom fusiform swelling of the elbow-joints was noticed during the second and third weeks of disease. One also had a swollen foot on which a sinus, yielding clear fluid, later appeared. One child was well-, and one ill-nourished; return of function in the former was more rapid and complete. Kini and Kesavaswamy (1941) in India, in 11 years, collected 21 cases of involvement of bones and joints after smallpox. Detailed case histories are not provided, but it appears that the great majority were late cases showing limb deformities. The development of these complications could not be predicted from the severity of the smallpox. The bone and joint lesions arose in the recovery period, with little constitutional upset. The authors emphasized arrest of growth as a sequel of the joint lesion.

Rivoalen (1948), in an important paper from Indo-China which he entitled 'Osteoarthropathy in Smallpox', remarked that 'this complication has fallen into oblivion recently'. In an epidemic of 283 cases of smallpox he discovered 18 cases of arthropathy, all in children under the age of six years. All were unvaccinated or too recently vaccinated for protection. He considered the primary lesion to be due to the smallpox virus, sometimes complicated by secondary infection, and commented on the absence of toxaemia, in contrast with pyogenic osteomyelitis. He described three clinical types of the disorder. The rarest was a simple osteomyelitis without joint involvement; he saw only one such case. The second was a simple arthritis, arising about the 15th day after the eruption with swelling of the joint and a slight rise in temperature. The elbows were always involved first, often followed by other joints. No lesion could be discerned by X-rays, and these cases settled down with full return of function within three weeks. The third type, which he denoted as 'suppurative osteoarthritis', was seen to occur especially in under-nourished, anaemic children. The onset was between 10 and 30 days after the smallpox eruption. The lesion, which was often symmetrical, consisted of a diffuse swelling around affected joints with thickening of adjacent bones. X-rays showed destructive metaphyseal lesions with periostitis. Three patients, all in advanced cachexia, died, and in one of these autopsy showed the diaphysis to be full of pus, with numerous sequestra and disappearance of intra-articular portions of the bone. There was some extension of inflammation from the joint into the surrounding soft tissues. There was a remarkable tendency to recovery, but fever might persist for weeks, and ankylosis or subluxation of joints sometimes followed. Some permanent limitation of movement was usual. In the whole group the elbow-joint was involved 16 times, the next in frequency being the shoulder, ankle, knee, and wrist. The humerus, radius, and ulna were the bones most frequently involved. Other aspects of this epidemic were discussed by Nhan-Thuan (1943).

From Indonesia Wiersema (1950) reported three cases. He, too, believed that

the cause of symptoms was a disease of bone due to the smallpox virus, and deduced from X-rays that foci within the bones, each about 1 cm. long, were the inflammatory units responsible. Subsequent function of the affected joints often exceeded expectation, but disabilities that persisted seemed to involve the legs more than the arms. X-ray appearances were always worse than would be expected clinically. The epiphyseal centres in the neighbourhood of affected joints were reduced in size, and might disappear. In the metaphyses coalescing lacunae of osteoporosis made the epiphyseal border very irregular; further up the shafts uneven sclerosis of bone was evident. Periosteal new bone formation, disproportionate to the underlying changes, was observed sometimes to extend far along the diaphysis. Different bones concerned in a single articulation might be affected to quite different degrees. The epiphyses were most severely damaged in young children; with increasing age the diaphysis was more severely implicated.

Chatterjee (1950) regarded arthritis as one of the most serious complications of smallpox. In a 1948 epidemic in Calcutta there were 2,341 cases; 115 patients were under the age of 10 years, and 10 of these children developed arthritis. In every case the elbows were involved, generally bilaterally. Lesions in other joints, when present, developed two to three days later. Chatterjee noticed that arthritis did not occur in confluent cases of smallpox, but in patients with discrete lesions at the scaling stage, that is about three or four weeks after onset. Joint symptoms began abruptly, with pain and fever but negligible toxaemia. The joints were painful only on movement, and not to the same degree as in septic arthritis. Joint fluid was sterile, except where sinuses were present. The swelling appeared in part to be periarticular. Sometimes a joint would burst and give rise to a sinus. Radiological changes consisted of epiphyseal destruction and new bone formation, and were most commonly evident in the head of the radius, next in the upper end of the ulna, and least often in the lower end of the humerus. There was no reduction in width of the joint space. Banerjee (1952), who saw 21 cases of what he termed 'suppurative osteomyelitis' in the 1951 smallpox outbreak in Calcutta, reported a rather different experience. Although 18 of his patients were under six years of age, three were over 20. In half of these cases swelling and fever developed within the first month after smallpox, but in the remainder after that period. Joint involvement was not predominantly of the elbows. The X-ray appearance was that of pyogenic osteomyelitis, and epiphyseal damage was seen only twice. Banerjee considered his cases to be pyogenic infections, due to a coccal septicaemia occurring in a phase of lowered resistance after smallpox, and we must agree that, as described, they do not tally with other accounts of osteomyelitis variolosa.

In 1953 Hébraud, Nicol, and Rannou, discussing surgical complications of smallpox in Tunis, referred to a girl of seven years who developed bilateral elbow swellings on the 18th day of smallpox, and a boy of 12 with an apparently aseptic necrosis of the clavicle, without joint involvement, which started on the 30th day of his disease. Bertcher (1956), writing from Korea, gave an

TABLE I

Summary of Findings in Fifteen Nigerian Patients with Osteomyelitis Variolosa

Case number	Age (years)	Sex	History of vaccination	Interval between smallpox and joint symptoms	Chemotherapy before onset of joint symptoms	Regions affected clinically	Sinuses	Bones affected radiographically	Results of aspiration			Blood examination			Follow-up period	Result
									Joint	Examination	Culture	Haemoglobin %	White cells; cu. mm.*	Sickling		
1	7/12	M	Successful vaccination 10 days before smallpox	4 weeks	Nil	Left elbow; right foot and ankle	Left elbow	Left humerus, radius, ulna; right fibula	Elbow	Thick green pus: variola elementary bodies	*Strep. pyogenes*	35	19,500 P. 59%	Negative	4 weeks	Slight improvement
2	1	M	Unvaccinated	2 weeks	Nil	Left elbow	Left elbow	Left humerus, radius, ulna; right humerus, 5th metatarsal	..	..	..	70	..	..	12 weeks	Considerable improvement. Sinus healed.
3	1	M	Unvaccinated	1½ weeks	Nil	Both elbows, wrists, hands, feet	..	Both humeri, radii, ulnae, tibiae, fibulae	Ankle	Thick pus; variola elementary bodies	*Staph. pyogenes*	47	10,600 P. 73%	Negative	6 weeks	No change
4	1	M	Unvaccinated	1½ weeks	Sulphadimidine	Right elbow; right index finger	..	Right humerus, radius, ulna	..	..	..	..	..	..	2 weeks	Complete clinical recovery
5	1½	F	Unvaccinated	3–4 weeks	Nil	Both elbows	..	Both humeri, radii, ulnae	Elbow	Thin pus	Sterile	39	..	..	10 weeks	No change
6	1½	M	Unvaccinated	3 weeks	Penicillin injections	Both elbows	..	Both humeri, radii, ulnae	..	..	..	..	..	..	1½ weeks	Recovery almost complete
7	1½	F	Unvaccinated	4 weeks	Nil	Left elbow; both feet and ankles	Right foot	Left humerus, radius, ulna; right 1st metatarsal; both calcanei and 5th metatarsals	Elbow	Pus	Sterile	..	..	Negative	8 weeks	No change
8	2½	F	Unvaccinated	4 weeks	Nil	Both elbows; both ankles	Left ankle; left wrist	Both calcanei; left talus; both humeri, radii, ulnae	..	..	..	..	..	..	None	..
9	3	M	No record	2 weeks	Nil	Right arm and elbow	..	Nil	..	..	..	64	9,600 P. 64%	..	3 days	Died of bronchopneumonia
10	3	F	Unhealed vaccination present at onset of smallpox	1½ weeks	Sigmamycin	Both elbows	..	Both humeri, radii, ulnae	Elbows	No fluid obtained	..	20	..	..	2 weeks	No change
11	5	M	Vaccinated 2 days before smallpox	A few days	Procaine penicillin	Both elbows	..	Right radius and ulna	Elbow	Pus; variola elementary bodies	Sterile	..	14,400 P. 75%	..	None	..
12	6	M	No record	3 weeks	Nil	Both elbows	..	Both humeri, radii, ulnae	..	..	..	..	..	..	None	..
13	6	F	Successful vaccination 1 day before smallpox	3 weeks	Sulphadimidine	Both elbows	..	Right radius and ulna; left ulna	..	..	..	..	..	..	2 weeks	Considerable improvement
14	7	F	Unvaccinated	1 week	Sulphadimidine	Both elbows	..	Both humeri, radii, ulnae	Elbow	Thin blood-stained fluid; variola elementary bodies	Sterile	..	..	Negative	6 weeks	Considerable improvement
15	17	M	Unvaccinated	2 weeks	Sulphadimidine	Left elbow; left leg	..	Left radius and ulna; left fibula	Elbow	Thin pus	Sterile; smallpox virus not grown	..	..	..	None	..

* P. = polymorphonuclear cells.

account of six cases of osteomyelitis variolosa with joint swellings affecting the elbows alone (in two cases), the knees alone (in one case), or both together. All six patients were three years of age. Though clinically the condition might appear to be unilateral, X-rays revealed a bilateral lesion in every case. The epiphyseal lines were not much affected, but extensive periosteal new bone was seen sheathing the shafts of the bones. After three months considerable remodelling had occurred. Symptoms subsided without treatment, and function was fairly good, but swelling was still detectable in one child four months later. Bertcher remarked that 'the bone disease of variola results most probably from invasion of bone at the time of initial viraemia. Probably it is only when the child recovers sufficiently to walk or move the limbs that complaints referable to joints appear.'

Nigerian Epidemic

In Table I we summarize the principal findings in our 15 cases. Since these were collected, a further five children with this disorder have been seen, but are not included. It should be noted that of the 15 patients all but one were children under 10 years, that the elbows were involved, singly or together, in every case, that seven patients had received some chemotherapy in the early stages of smallpox, and that in four cases elementary bodies of variola were demonstrated in the joint aspirate.

Clinical Features of Osteomyelitis Variolosa

After studying the foregoing published accounts and our own observations, it is possible to conclude that bone and joint complications of smallpox are of two types, namely:

1. Ordinary pyogenic osteomyelitis, which may occur, as Brown and Brown (1923) remarked, in any acute infectious disease. We saw no instance of this increasingly rare complication, and we are not concerned with it in the present paper.
2. Osteomyelitis variolosa. We have adopted this name in preference to 'smallpox osteoarthropathy' or 'osteoarthritis', not only because it appeared early in descriptive writings, but because we believe it to be a correct description of the underlying lesions, and also because 'osteoarthropathy' is not sufficiently precise, and 'osteoarthritis' has become inseparable from degenerative joint disease. Osteomyelitis variolosa may declare itself as a lesion confined to bone. We did not observe such an occurrence, and it is certainly much less usual than the arthritic type of onset. Nevertheless, we believe that accompanying bone disease, whether clinically evident or not, is present invariably, and is the basic lesion. Either clinical variety may be complicated by secondary bacterial infection. In order to review the clinical findings we discuss our own cases in conjunction with those previously published (Table II).

TABLE II

Published Cases of Osteomyelitis Variolosa

Authors	*Date*	*Number of cases*	*Sex*		*Lesion*	*Age at onset (years)*				*Sites involved*
			M	*F*		*0–5*	*5–10*	*10–20*	*over 20*	
Kolaczek	1875	1	1	..	Osteomyelitis and arthritis	..	..	..	1	Clavicle; both elbows
Neve	1887	2	..	..	Osteomyelitis	2	..	..	..	(1) Ulna; (2) scapula
		2	2	..	Arthritis	1	1	..	..	(1) Elbows and wrist; (2) shoulder
Ingelrans and Taconnet	1903	3	..	1	Osteomyelitis	..	..	..	1	(1) Tibia; (2) radius; (3) clavicle (died)
Debeyre	1903	1	..	..	Osteomyelitis	..	..	..	1	Humerus
Musgrave and Sison	1910 1913	20	8	4	Late deformities	Latest age at which smallpox occurred: 14 years				Elbows 19 cases, with wrists 6 times, hands twice, knee once, foot once, temporo-mandibular joint once; wrist and hands one case
Cango	1912	3	..	..	Late deformities	..	..	..	..	Hands and forearms
Schwenk	1912	1	..	1	Late deformity	..	1	..	..	Both shoulders
Sheldon	1923	2	..	..	Late deformities	..	..	..	..	(1) Forearm and elbow; (2) ankle and lower leg
Brown and Brown	1923	2	..	..	Late deformities	2	..	..	..	(1) Wrists, elbow, leg; (2) elbow
Cathcart	1924	2	1	1	Late deformities	2	..	..	..	(1) Elbows and wrists; (2) right arm
Huenekens and Rigler	1926	1	..	..	Polyarthritis	1	..	..	..	Wrists, ankles, elbows, knees, cervical intervertebral joint
Eikenbary and LeCocq	1931	3	2	1	Late deformities	1	2	..	..	(1) Elbow, hand, wrist; (2) knee; (3) knee
Long, Nguyen Khac-can, and Nguyen Phan	1938	1	..	1	Arthritis	..	..	1	..	Elbows and knees
Navasimhan	1940	16	9	7	Arthritis	8	3	1	..	Elbows 13 cases, with wrist twice, hip once, knee once, fibula once; knee one case; ankle one case; temporo-mandibular joint one case
							'Childhood', 4			
Fan	1940	2	2	..	Arthritis	2	..	..	..	(1) Elbows and foot; (2) elbow
Kini and Kesavaswamy	1941	21	..	..	Mainly late deformities. No details	..	..	..	..	..
Rivoalen	1948	18	8	10	Arthritis	17	1	..	..	Elbows 16 times; shoulders 6 times; ankles 6 times; knees 5 times; wrists 4 times; metacarpo-phalangeal joints twice; hip once; temporo-mandibular joint once
Wiersema	1950	3	1	2	Arthritis	2	1	..	..	(1) Elbow and wrist; (2) elbows, knees, wrist, shoulder; (3) elbows
Chatterjee	1950	10	2	8	Arthritis	All under 10 years		..	..	Elbows all cases, bilaterally in 7
Banerjee	1952	21	12	9	Osteomyelitis and arthritis	18 under 6 years		..	3	No details
Hébraud, Nicol, and Rannou	1953	2	1	1	Arthritis	..	1	1	..	(1) Elbows; (2) clavicle
Bertcher	1956	6	3	3	Arthritis	6	..	..	..	Elbows 5 cases, knees 4 cases
Cockshott and MacGregor	1958	15	9	6	Arthritis	11	3	1	..	Elbows 15 times; ankle and foot 5 times; wrist and hand twice

1. *Age at onset.* Children are affected almost exclusively; the great majority have been less than five years of age, but infants are not exempt. The oldest certain case of the arthritic type was Kolaczek's (1875) at 21 years old. Affected adults have as a rule suffered from osteitis without joint involvement.

2. *Sex incidence.* Of the patients whose sex was stated, 61 were male and 55 female.

3. *Vaccination history.* Whenever information has been supplied, patients with this complication have proved to be unvaccinated or vaccinated too recently for protection.

TABLE III

Published Observations on the Incidence of Osteomyelitis Variolosa

Author	*Year*	*Cases of osteomyelitis*	*Cases of smallpox observed*	*Years of observation*	*Country*
Neve	1887	'Common locally'		..	Kashmir
Ingelrans and Taconnet	1903	3	500	..	France
Anon. (quoted by Ingelrans and Taconnet)	1903	0	300	12	France
Fan	1940	2	..	10	China
Kini and Kesavaswamy	1941	21	..	11	India
Rivoalen	1948	18	283	..	Indo-China
Wiersema	1950	'More common locally than it used to be'		..	Indonesia
Anon. (quoted by Wiersema)	1950	7	2,500	..	Indonesia
Chatterjee	1950	10	2,341 (115 under 10 years)	..	India
Cockshott and MacGregor	1958	20	2,500	..	Nigeria

4. *Incidence.* Figures indicating the views of various workers on this point are given in Table III. There is a wide range in the calculations, and the estimated incidence must of course depend upon how many of the smallpox patients are children. As a very rough guide one may say that the complication affects from 0·25 to 0·5 per cent. of patients in a smallpox epidemic, while 2 to 5 per cent. of affected children are liable to be attacked. It is doubtful whether many subclinical cases of this osteitis occur. We took X-rays of the elbows of a number of children with uncomplicated smallpox, thus repeating the experiment of Huenekens and Rigler (1926), with a similar negative result.

5. *Frequency of clinical types.* (1) *Bone disease alone.* Cases of osteitis without joint inflammation have been recorded by Neve (1887), Ingelrans and Taconnet (1903), Debeyre (1903), Sircar (1912), Rivoalen (1948), and Hébraud, Nicol, and Rannou (1953). Such infections have been clinically quiet, with a satisfactory outcome, and terms such as 'low-grade', 'aseptic necrosis', and 'smouldering infection' have been used to describe them. Like Wiersema (1950), we have sometimes noticed in X-rays that bones remote from affected joints were diseased, as for example the fibula in Case 15, but on the whole it has been older children or young adults who have exhibited this type of illness. (2) *Arthritis.* Except for those just mentioned, all patients have had one or more joints involved.

6. *Severity of antecedent smallpox.* It has several times been noted that this complication occurs as readily after mild as after severe smallpox. Confluent smallpox is unusual in children, which accounts for the constancy of a non-confluent eruption in cases of osteomyelitis. The state of nutrition of affected children has varied from appalling to excellent, and it is certain that neither good nutrition nor mild smallpox will necessarily confer protection. It was pointed out by Neve (1887) and Rivoalen (1948) that grave malnutrition and anaemia predispose to some extent, and it is of interest that five of our children (Cases 1, 3, 5, 10, and 13) were grossly anaemic, with signs of protein malnutrition. Other complications of smallpox have seldom been noted together with osteomyelitis variolosa. Cutaneous abscesses have been occasionally mentioned, and in our series there was one death from bronchopneumonia.

7. *Time of onset.* Others besides ourselves have often found it difficult to be precise about the time of onset of the complication. In the first place, the serious nature of smallpox itself overshadows incidental symptoms; further, the arthritis has frequently begun very quietly; and, finally, the patients have in the main been illiterate, with an undeveloped time sense and limited powers of observation. It is clear, however, from a study of the whole group of recorded cases, that there is nearly always a latent interval of between one and six weeks between the onset of smallpox and the appearance of joint symptoms. In most cases arthritis has been first noticed from 10 days to four weeks after smallpox has begun. Very occasionally joint symptoms have been seen in the first few days of the disease, as in the case described by Huenekens and Rigler (1926), and in our own Case 11.

8. *Joints attacked.* It is generally agreed that joints are frequently involved symmetrically, and that the elbows are by far the most common site. Nearly every joint in the body has been implicated, but among the 124 cases of which we have details the elbow joint was involved on one or both sides in 97. Next in frequency were the wrist and hand (25 cases), ankle and foot (16 cases), and knee (17 cases). In rather over half of the patients joints were affected at more than one site.

9. *Symptoms and signs.* Swelling round a joint was nearly always the first sign. Though there might be a little pain at the onset, it was sometimes lacking, and difficulty in movement was first noticed. Once the swelling was established, local tenderness and pain on movement of the joint were usual. When more than one joint was affected, there was often an interval of a day or two between their successive involvement. The elbows were usually implicated before any other joint. Effusions into the joint were not demonstrable in very mild cases, although there was periarticular swelling. Usually, however, effusions were of moderate size, and the affected joints were surrounded by fluctuant, tender, fusiform swellings, which could be seen and felt to extend as a boggy sheath over the portions of the bones contiguous with the joint. Sometimes, particularly in the arm, the contours of a limb were obliterated by a swelling extending upwards and downwards to the neighbourhood of proximal and distal joints. The underlying bones in such cases would be felt to be thickened and irregular.

They were never tender. When hands and feet were involved, the soft tissues over affected bones became grossly swollen and tense (Plate 38, Figs. 1, 2, and 3). Limitation of movement of the affected joint was always the major disability. In severe cases disorganization of joints (especially of the elbows) was apparent in abnormal mobility and crepitus on movement. Large effusions sometimes formed sinuses, which would continue to discharge thin or frankly purulent fluid. Sinuses were usually sited over joints, but were sometimes seen over the metaphyses of bones, and the extrusion of a sequestrum has been more than once observed.

A low fever, up to 102° F, was not uncommonly observed, from the time of onset of the joint symptoms for as long as six weeks. In other cases the course was non-febrile throughout. A minor leucocytosis, up to 20,000 cells per cu. mm., with a preponderance of granulocytes, was observed. It has been widely remarked that there is no toxaemia, or constitutional symptoms other than fever, attributable to the joint disease, and this fact was also noteworthy in our patients. The condition is an uncomfortable interference with function rather than an illness.

We looked for sickling of the red blood-cells in four of our patients, but it was not present. Sickle-cell anaemia is common in Ibadan, and an observed association, both in our wards and in the medical literature (Vandepitte, Colaert, Lambotte-Legrand, and Perin, 1953; Golding, 1956), between this disorder and osteitis due to salmonella infection, caused us to inquire whether the bones of sickle-cell patients were at special risk in smallpox also.

10. *Radiographic features.* The following account is based upon radiological study of our 15 cases, supplemented by a further five patients who were referred to us for radiological examination only. Our interpretation of the results is in general accord with most published descriptions. In our series the radius was affected 28 times, the ulna 26 times, humerus 19 times, metatarsals seven times, fibula and os calcis six times, tibia and talus five times, and metacarpals three times. It differs from previous series in that none of our children showed involvement of the knee or shoulder. Five of our patients had radiographs taken of their elbows before any changes were apparent, but serial examination usually provided evidence of the later development of lesions and of their progress.

The changes will be described as they occur in the elbow of a typical case. This composite picture is fairly faithfully reproduced in individual cases, though subject to some variations. The chief cause of variation is that in the younger patients much of the extremities of bones is composed of cartilage, and is therefore not directly visualized, so that changes there can only be inferred. At the earliest stage all that was noticed in the film was swelling of soft tissues around the joint, with perhaps indirect evidence of a joint effusion. Next, a band of osteoporosis was seen in the perimetaphyseal region, sharply demarcated on the epiphyseal side, but less well defined on the diaphyseal aspect of the metaphysis (Plate 39, Figs. 6 and 7). In the younger children without bony epiphyses a thin cap of intact bone remained at the epiphyseal end of the metaphysis, in

contrast to the destruction of the diaphyseal aspect (Plate 39, Fig. 4; Plate 40, Fig. 8). The area of bone destruction differed from that seen in the perimetaphyseal focus of classical pyogenic osteomyelitis in that it traversed the bone as a band from the start, and was not situated to one side. The above changes were most readily detected in the proximal end of the radius, but could be seen, though less readily, in the ulna and humerus in about two-thirds of the patients. A thin shell of periosteal new bone was next seen to extend along one or more of the bones comprising the articulation, and to invest the shafts (Plate 39, Fig. 5). This reactive change was limited, close to the joint, by the attachment of the capsule. In a few cases it was pronounced enough to form an involucrum. This sheath of bone became incorporated with the shaft within three months by moulding, and left some thickening of the diaphysis, especially near the capsular attachment, where bilateral spurs were frequent. A few patients also showed extensive patchy destruction of the shafts of bones, and later sclerosis, such as is seen in chronic pyogenic osteomyelitis. The joint line, far from being obliterated, was excavated in most instances (Plate 40, Fig. 9). Detachment or sequestration of the epiphysis is the lesion uniquely associated with this disorder, and seems to be the result of the transverse metaphysitis. It was not seen in every instance, but when present developed at an early stage, exemplified by some patients in whom the epiphyses were tilted, and in a few cases completely detached, when they were first seen (Plate 39, Figs. 4 to 7; Plate 40, Figs. 9 and 11). The loose bodies so formed gradually diminished in size, and appeared eventually to become absorbed. In some cases the epiphyseal remnants were extruded through sinuses. The tarsal bones, when involved, showed at first a patchy rarefaction, soon accompanied by a rim of periosteal new bone. Repair with sclerosis followed, but deformity was the rule (Plate 40, Fig. 10).

11. *Examination of joint fluid.* Fluid removed from joints has been found to be sterile in a great many cases. The common pyogenic organisms have sometimes been grown on culture, and when sinuses were present the joint was of course always secondarily infected. Elementary bodies of variola were detected in the joint fluid in four of our cases, and in two of these the joints were also infected with cocci.

12. *Treatment.* (1) *Before joint complications have arisen.* Seven of our patients received chemotherapy at an early stage (Table I). Some smallpox patients were medically supervised by the local authority in their villages, and these received sulphadimidine in full oral dosage for a week or 10 days from the time of diagnosis (Cases 13, 14, and 15). In addition, patients admitted to the Smallpox Hospital for treatment of the initial illness were often given chemotherapy. Two of our patients were given procaine penicillin, one sulphadimidine, and one 'sigmamycin' (a combination of tetracycline and oleandomycin). These drugs were administered for about a week. The bone and joint lesions in patients who had received such preliminary treatment differed in no way from those observed in untreated cases, a fact which argues strongly against a pyogenic cause. We cannot find any record of preliminary chemotherapy having been used in other published cases. (2) *Treatment of the joint complication.* Our

practice has been to correct malnutrition and anaemia, where present, by high-protein diet and blood transfusion respectively, to immobilize the affected joints with bandages and plaster of Paris, and in most cases to administer chemotherapy to combat secondary infection. In the present series chloramphenicol was used five times, penicillin and streptomycin together five times, chlortetracycline twice, and oxytetracycline twice. We have no reason to think that our patients so treated fared any better, as regards the duration of symptoms or the progress of radiographic changes, than those untreated, judged by our own experience and previous reports.

13. *Progress.* There is general agreement in the literature that the lesions described tend towards recovery, without treatment, in the course of a few months, and that the degree of eventual function is better than one might expect at the beginning. Nevertheless the complication is a serious one, with a considerable residue of crippling and deformity, as the numerous accounts of late sequels indicate. Even comparatively mild cases often leave a limitation in the movement of joints. Serious sequels depend upon epiphyseal damage or detachment, and consist in reduction, cessation, or aberration of the longitudinal growth of bones, with consequent shortening or distortion of limbs. Bony or fibrous ankylosis is probably caused by damage to the articular cartilages through secondary bacterial infection, and is uncommon. Our patients have not been followed up for long periods. In the literature there are very full accounts, which we have reviewed, of the outcome of the disorder. During a few weeks of observation all the mild or moderate cases in our series have shown clinical improvement. Swellings have diminished in size, sinuses have healed, movement has increased, and pain and tenderness have subsided. Apparent restoration to normal has occurred in three cases. In severe cases no improvement has been seen except in general nutrition. The outlook for joints in which epiphyses are separated or destroyed, and in which abnormal movements are present, is serious indeed. Such patients are now treated at home, and their affected joints are splinted with plaster of Paris to provide rest, give stability, and avoid pathological fractures.

Pathogenesis

Since the early years of this century it has been suspected that the lesion of osteomyelitis variolosa is not a pyogenic infection, but that the smallpox virus itself is responsible. This has been argued from the comparative absence of constitutional disturbance, from the latent interval between the exanthem and the joint symptoms, which has suggested a connexion with the primary infection, from the symmetrical epiphysitis peculiar to this disease, and from the absence of micro-organisms in aspirated joint fluid. The failure of preliminary chemotherapy to prevent the complication, and the presence of variola elementary bodies within affected joints, provide further evidence in favour of direct infection with smallpox virus, although virus from this site has not yet been grown in culture.

Virus lesions of bone, though unusual, are by no means unknown. Wright and Logan (1939) have described viral osteomyelitis in lymphogranuloma inguinale, and several cases are on record of osteomyelitis following prophylactic vaccination against smallpox. Sewall (1949) described osteomyelitis two weeks after primary vaccination of a 17-months-old girl, without toxaemia or appreciable local symptoms. Radiographically the shaft of the ulna showed destructive changes and periosteal bone formation. Vaccinia virus was obtained by culture from a biopsy of the lesion. Sewall cited another case known to him in which vaccinia virus was grown by culture from a bone lesion. Solito (1932) referred to a similar lesion in the shoulder of a nine-months-old child occurring 12 days after an otherwise uncomplicated vaccination. Of special interest was the X-ray appearance of the lesion, involving the epiphysis and metaphysis of the upper humerus and the adjacent glenoid margin of the scapula, in a manner reminiscent of the lesion in osteomyelitis variolosa. Clinical recovery was complete after 10 days, and X-ray appearances had returned to normal in four months. Brinkmann (1932) also recorded osteomyelitis after vaccination, and commented upon subsequent premature fusion of the epiphyses of affected bones. The three-months-old infant described by Delano and Butler (1947) presented a different clinical picture. Ten days after vaccination this child developed encephalitis, accompanied by lesions described as 'ossifying periostitis' in metatarsals, clavicles, humeri, and scapulae. The nature and course of the illness, which the authors believed to be vaccinial osteomyelitis, were very similar to Caffey's (1946) syndrome of infantile cortical hyperostosis, and the authors made the interesting suggestion that the latter illness also might represent a virus osteomyelitis. Proven bone lesions of vaccinia virus, therefore, have resembled those of osteomyelitis variolosa, even to the reproduction of its most unique feature, damage to the epiphysis. We consider that this circumstance substantiates the hypothesis of direct invasion of the skeleton by smallpox virus in osteomyelitis variolosa.

Proliferation of a virus during the incubation period of smallpox probably takes place in lymphatics draining the portal of entry (Bedson, Downie, MacCallum, and Stuart-Harris, 1955). Soon after this an initial viraemia occurs, which infects the entire reticulo-endothelial system, where further proliferation leads up to a secondary intensive viraemia ushering in the clinical illness. Except in fatal cases, virus does not remain in the blood-stream for more than two days. Infection of the skeleton with virus must therefore occur during either primary or secondary viraemia, before the appearance of the exanthem. Delay in the origin of joint symptoms might be only apparent, and manifestations of skeletal disease, although present, might be overlooked until convalescence. This theory was advanced by Ingelrans and Taconnet (1903) and by Bertcher (1956). We do not accept it, because of the general agreement about the length of the interval (10 days to four weeks) before the complication arises. This explanation could only be accepted, moreover, if all patients had been so gravely ill with smallpox that complications were obscured. It has already been pointed out that the severity of the smallpox bears little relation-

ship to the origin of skeletal complications; this was true in our own patients, in several of whom the primary illness was comparatively trivial. In our case histories, as in those of Chatterjee (1950), the date of origin of joint swellings could sometimes be stated exactly, as well as the order in which different joints became involved.

The contrary possibility is that the virus lies dormant within the bones or joints during the latent interval, thereafter becoming active and initiating the inflammatory lesion. Although antibodies, preventing further invasion of the blood-stream by virus, appear early in the disease, they are not lethal to virus present in the tissues. The infective agent in smallpox persists in skin lesions until the final stages, and may survive in dried crusts for over a year (van Rooyen and Rhodes, 1948). It is improbable, however, that a virus should awake to clinical activity at the moment when defensive antibody levels have reached their maximum and when, presumably because of this, tissue infection elsewhere in the body has been conquered. Resistance to fresh tissue infection has reached a considerable pitch by the sixth day of the illness, after which attempted vaccination is never successful (Bedson, Downie, MacCallum, and Stuart-Harris, 1955). Also counter to the idea that the stage of acute joint symptoms marks the genesis of a pathological process in the skeleton is the observation of disproportionately severe radiographic changes in bone very soon after the first complaint of joint swelling or pain, as in Cases 5, 6, 7, 12, and 13. We prefer to believe that acute symptoms and signs arise at a certain stage in the evolution of a skeletal lesion, of which the onset is simultaneous with the primary exanthem. There is every reason to think that the osteitis is clinically silent, for, in spite of gross changes in the bones, pain is never sited over them, but is centred upon the swollen joints. It is only when exudation occurs in and around the joints that pain, swelling, and fever are experienced.

We believe that the metaphysis of a bone is the area first affected, and that some time is occupied in spread of the inflammation from this region to the intra-articular bone surface, from which the synovial membrane is infected. This is preferable to the hypothesis that the synovia is infected at an early stage, but that exudate into the joint only develops after two or three weeks, an evolution that would not agree with the behaviour of smallpox elsewhere in the body. The involvement of joints seriatim, and not all together, negates any idea that effusions are an allergic manifestation, either in response to virus protein or in the course of antibody-antigenic reactions. Recorded examples of synovitis without osteitis (Kini and Kesavaswamy, 1941; Rivoalen, 1948) were mild cases, in which serial X-rays would probably have shown the development of bone changes. In some of our own patients (Cases 3, 4, 9, 11, and 14) no bony lesion was seen on first examination, but such lesions eventually appeared in the three in whom subsequent X-rays were possible. When symptoms were clinically confined to one elbow (Bertcher, 1956, and our Case 2) bilateral bone changes were sometimes demonstrable, a fact which also supports antecedent bone infection.

Confirmation of this hypothesis cannot be obtained in the realm of morbid

histology because, unfortunately, information about bone pathology in smallpox is meagre. Recognizable specific lesions occur in certain viscera, the testes for example, in which nodules of tubular necrosis, with infiltration of wandering cells, can often be found. Such lesions are also seen in the liver, and occasionally in other organs (MacCallum, 1940). In 1893 Chiari published a much-quoted account of an examination of the bones of 22 patients who had died at three different stages of smallpox. In 19 of them he found disseminated necrotic areas in the bone-marrow, present in all stages of the disease; the cellular changes in these areas were identical in appearance with the nodular lesions of the testicle. The process was non-suppurative. Mallory (1894) observed three cases of smallpox at autopsy after the suppurative stage had been passed, and found circumscribed inflammatory foci with central necrosis, such as were described by Chiari. From Indonesia Bras (1952) described in detail 177 autopsies in the 1949 outbreak of smallpox. Over a score of cases of arthritis were observed during the course of the epidemic, but histological examination of the joints in patients who died without arthritis revealed no abnormality. The bone-marrow of lumbar vertebrae and femora was examined in 34 instances. In none were any significant foci seen such as Chiari described; small haemorrhages were the only finding. Bras cast doubt upon Chiari's interpretations, and surmised that he was mistaking post-mortem changes for ante-mortem lesions. Even if Chiari's findings are accepted, it is unlikely that they can have any bearing on the subject we are discussing, for they were alleged to be fairly regularly present in cases without bone and joint disease. Pathological observations upon cases of clinical osteomyelitis variolosa are regrettably scanty, and are limited to the reports of Musgrave and Sison (1913) and Rivoalen (1948), which have already been cited. A synovial biopsy performed in our Case 1, about eight weeks after the onset of arthritis, merely showed granulation tissue heavily infiltrated with polymorphonuclear cells and lymphocytes. The finding of variola elementary bodies in the joints of four of our patients attests the presence of virus within them.

Our conception of the pathology of osteomyelitis variolosa must be based, therefore, upon deductions from clinical and especially from radiological findings. We have already expressed our belief that the primary site of bone invasion is the metaphysis. It appears that the metaphysis, in the stage of active growth in early childhood, is especially vulnerable, and that the epiphyseal centre of ossification may become detached or destroyed. It is significant that this lesion is never seen after adolescence, a fact which suggests that the proliferating cartilage-cells of the epiphyseal junction are attacked. From here infection spreads in all directions, along the shaft of the bone, externally to the periosteum, and to the capsular attachment of the neighbouring joint, with consequent synovial infection. The articular cartilage is not eroded unless there has been secondary infection. There need be no surprise at a viral inflammation of a synovial membrane, in view of the ready growth of variola upon the chorioallantoic membrane of the chick embryo. It must be from cells of the synovial membrane that elementary bodies within the joint are derived. The deductions

of Wiersema (1950), which have already been referred to, about the nature and spread of lesions within the bone, are interesting. Much confusion in classifying osteomyelitis variolosa, and in recognizing its origin from virus infection, has stemmed from the discovery of pus within the joints and within affected bones. Our own studies agree with others in showing that purulent fluid withdrawn from such joints is often sterile on culture. Modern opinion holds that secondary infection by bacteria is of little importance in producing the pathological picture of the pustular stage of smallpox (Bedson, Downie, MacCallum, and Stuart-Harris, 1955), so that it is not unreasonable to suppose a similar invasion by polymorphonuclear leucocytes of bones and joints affected by smallpox virus. Secondary invasion by pyogenic organisms, entering either through sinuses or from infected skin lesions via the blood-stream, might be expected occasionally to complicate the picture of this virus osteoarthritis. Such a complication occurred in Cases 1, 3, 7, and 8, and has often been reported. In Cases 1 and 3 joint fluid, besides yielding a pyogenic organism on culture, revealed variola elementary bodies on microscopy. It is surprising that such secondary infection does not disseminate, and seems to cause little toxaemia. Secondary infection is, however, a serious local hazard, as it may lead to destruction of the articular cartilage and further grave impairment of joint function.

It remains to consider why the elbow joints are predominantly selected for attack. For this we cannot put forward any satisfying hypothesis. Vigour of epiphyseal growth cannot be the reason, for the epiphyses at the proximal end of the humerus and distal ends of the radius and ulna are more active than those at the elbow. Minor traumata, by friction or pressure, are known to provoke a dense local distribution of smallpox upon the skin, and we suggest that extra strains and stresses upon epiphyseal lines, at a time when virus is circulating in the blood, may single them out in the same way for selective attack. The elbow at all times has a greater range of movement in two planes than any other distal limb joint. Furthermore, during the pre-eruptive phase of smallpox, when the patient is ill and recumbent, the forearms are inevitably moved more freely than the knees or other joints, and through a great range. Perhaps, therefore, the greater activity of the elbow at a critical time inflicts upon the metaphyses close to it the minor stresses which invite the smallpox virus to settle there.

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Summary

1. The medical literature bearing upon an insufficiently known skeletal complication of smallpox has been collected, and is described.

2. An epidemic of smallpox in Nigeria in 1957 provided 15 fresh examples of this condition in children, which are described. We have designated the condition osteomyelitis variolosa, following Brown and Brown (1923).

3. An account of the clinical and radiological features of the disorder, gathered from these several sources, is presented.

4. The pathogenesis of the disorder is considered, and reasons are advanced for regarding it as a primary infection of the metaphysis of growing bones by the virus of smallpox.

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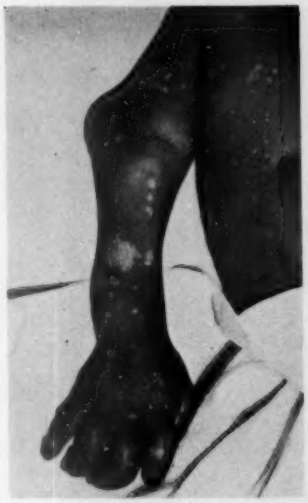

FIG. 1. Case 3. Right arm, showing swelling of the elbow, wrist, and fingers

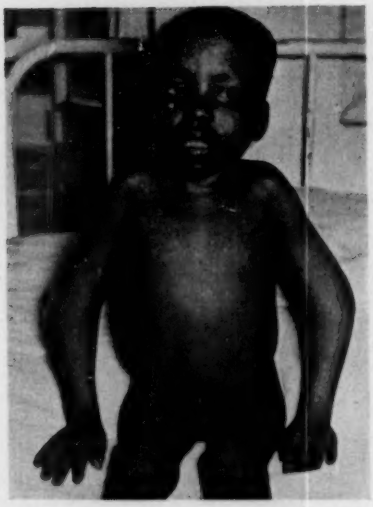

FIG. 2. Symmetrical swelling of the elbows in Case 13

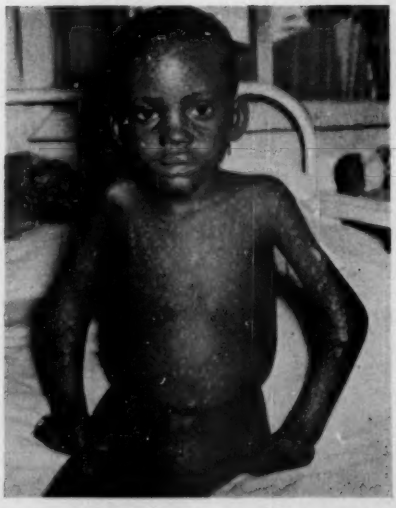

FIG. 3. Case 14. Healed exanthem and fusiform swelling of the elbows

FIG. 4. Case 2. Left elbow. The lower humeral epiphysis is displaced posteriorly. A transverse band of perimetaphyseal destruction capped by a rim of intact bone can be seen at the proximal end of the radius. The diaphyses are invested with periosteal new bone

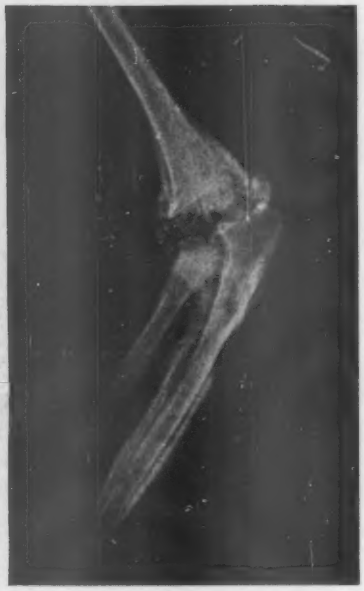

FIG. 5. Case 2. Left elbow two weeks later. Further disorganization of the joint has occurred. The lower humeral epiphysis has become a loose body. An involucrum has formed round the ulna.

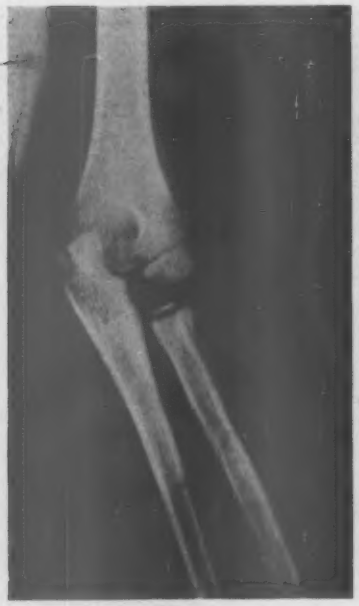

FIG. 6

FIG. 7

FIGS. 6 and 7. Case 14. Both elbows, 16.4.57, showing symmetry of the lesions

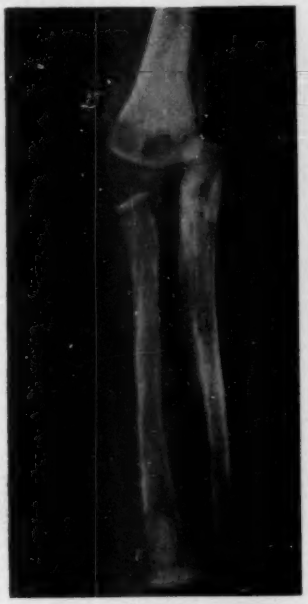

FIG. 8. Case 3. Right elbow, 7.3.57. Metaphyseal osteoporosis of the head of the radius and distal humerus, with osteitis of the radius and ulna. The joint is disorganized

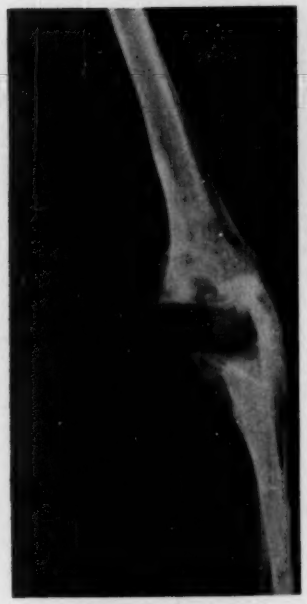

FIG. 9. Case 3. Right elbow, 5.6.57. A flail joint, lacking epiphyses. Excavation of the ulnar articular surface

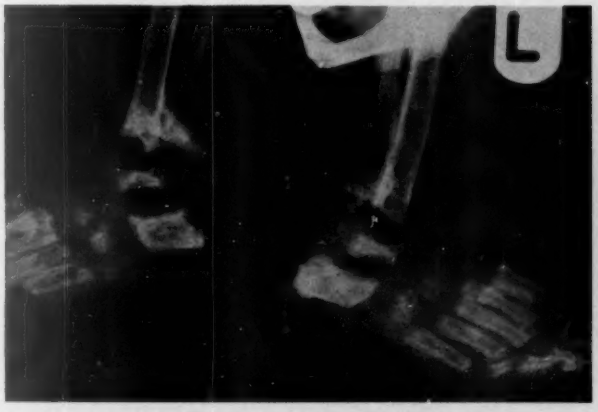

FIG. 10. Case 3. Both ankles, 5.6.57. Symmetrical deformity of the tarsal bones and disorganization of the ankle joints

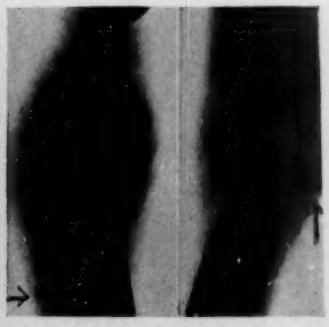

FIG. 11. Case 5. Both elbows, 28.1.57. The arrows indicate the position of the lower humeral epiphyses

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HEPATIC AMOEBIASIS[1]

A Study of 250 Cases

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With Plates 41 to 44

The clinician's concept of amoebic liver disease appears to be at variance with that of the pathologist. Current textbooks of medicine describe two separate entities, 'hepatitis' and 'abscess'. The following quotations imply not only that hepatitis is the pathological precursor of abscess, but also that each is a clinically recognizable entity:

'No clear-cut distinction is warranted, as they differ only in degree' (Harrison, 1954).

'The clinical picture in hepatic amoebiasis depends on whether the hepatitis has gone on to frank abscess or not' (Price, 1956).

'When an amoebic hepatitis is diagnosed early, before abscess formation, the response to emetine is very rapid and gratifying' (Davidson, 1953).

A description of 'amoebic hepatitis' is not to be found in standard textbooks of pathology such as those of Muir (1951), Boyd (1943), and Anderson (1953). Kean (1955) failed to identify a diffuse hepatitis, in which *Endamoeba histolytica* could be detected, in 4,478 autopsies in the Panama Canal Zone, or in 148 patients who had died from amoebiasis, or in 50 liver biopsy specimens from patients diagnosed clinically as having 'amoebic hepatitis'. In support of his own findings he quoted the work of da Silva (1950) in Singapore and of Donoso, Amenabar, Zacarias, and Rojas (1952) in Chile; these authors had also failed to demonstrate such a hepatic lesion in a combined total of 15,000 autopsies.

Chatgidakis (1953), however, described a single case of 'amoebic hepatitis' (with amoebae identified) occurring among 157 autopsies of patients who died from amoebiasis. Eighty-seven of these patients had liver abscesses. The patient described had a generalized peritonitis associated with a perforation of the colon and extensive amoebic ulceration of the large bowel—a picture which has often been encountered in this hospital. It is reasonable in this case to presuppose a gross invasion of the portal circulation by bacteria, debris, and the *Endamoeba histolytica*—in fact, a portal pyaemia. The hepatitis described by Chatgidakis could then perhaps be viewed as a complication of the general peritonitis, with secondary portal invasion by amoebae together with other bowel organisms, rather than as an actual amoebic hepatitis. Furthermore,

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such a clinical and pathological background can be considered as unusual in the average 'uncomplicated' case of amoebic liver disease. Chaudhuri and Saha (1956) reported a liver biopsy study of 15 cases of active amoebic dysentery. They described certain non-specific inflammatory changes in some of their cases, with round-cell infiltration of the portal tracts and over-activity of the Kupffer cells, but neither identifiable amoebae, nor any hepatic reaction specific for amoebic invasion of the liver, were demonstrated. Similar hepatic lesions were described by Dunlap, Dockerty, and Waugh (1954) in a liver biopsy study of 88 patients suffering from surgical disorders of the upper abdomen (other than amoebiasis). Imboden and Beye (1955) stated: 'It is commonly noted that a moderate degree of tender or non-tender hepatomegaly often accompanies acute or chronic intestinal amoebiasis without other clinical or laboratory evidence of hepatic involvement. It is the usual experience to observe resolution of this finding on successful treatment of the bowel infection, even though the drug used is active only within the bowel lumen. It is moot as to whether this manifestation is actually related to true hepatic amoebiasis.' Elsdon-Dew (1955) has long suspected that enlargement of the liver associated with intestinal amoebiasis occurs without actual infestation of the liver by the parasite.

It is thus evident that the nature of hepatic amoebiasis, in its various forms, is surrounded by considerable uncertainty and conjecture. There seems little pathological evidence of 'amoebic hepatitis'. Because of the abundance of amoebic liver disease in this hospital (the 250 cases surveyed are a selected group assembled over a period of only 15 months), it was decided to study the condition in the hope that some clarification might be achieved. Selection resulted from the fact that certain cases were discarded owing to incomplete investigation—a consequence of the need to maintain a rapid turnover of patients. The more serious cases, in which the patients stayed longer in hospital, were therefore included.

The Clinical Syndrome of Amoebic Liver Disease

From his extensive clinical and pathological studies, Kean (1955) has defined the syndrome of 'amoebic hepatitis' as consisting of:

1. An enlarged tender liver associated with fever;
2. A response to specific anti-amoebic therapy;
3. Moderate leucocytosis and laboratory evidence of disturbed hepatic function;
4. A history of intestinal amoebiasis.

In the present study 200 patients were specifically questioned as regards Kean's fourth criterion, and 110 (55 per cent.) denied any previous episode of diarrhoea, let alone dysentery. Such a history was therefore not included as a criterion in the present survey. The value of radiology in the diagnosis of hepatic amoebiasis has been stressed by Ochsner and DeBakey (1943). We are in a position to confirm this view in the present analysis, and suggestive radio-

logical findings have therefore been included as an additional criterion. For the present survey, therefore, the five diagnostic criteria adopted were:

1. A tender enlargement of the liver;
2. A response to specific anti-amoebic therapy (emetine and chloroquine);
3. Suggestive haematological findings;
4. Suggestive radiological findings;
5. The demonstration of pus, either by aspiration or by rupture into an adjacent viscus or serous cavity.

TABLE I

Incidence of Diagnostic Criteria in 250 Cases of Amoebic Liver Disease

Number of criteria satisfied	*Tender enlarged liver*	*Response to specific treatment*	*Positive blood findings*	*Positive X-ray findings*	*Pus by aspiration or rupture*
5	99	99	99	99	99
4*	104	102‡	92	89	29
3†	47	47	26	13	8
Total	250	248§	217	201	136
Percentage	100	99·2	86·8	80·4	54·4

* This group includes four patients not subjected to X-ray examination, and seven in whom the blood findings were not recorded.

† This group includes five patients with positive X-ray findings but no blood findings recorded, two with no X-ray or blood findings but pus obtained on aspiration, and four with negative X-ray findings, no blood findings recorded, but pus obtained on aspiration.

‡ Two patients did not receive anti-amoebic therapy, the diagnosis in both cases being made at autopsy.

§ Includes 14 of the 16 fatal cases, some initial response to treatment having been noted.

No case was included in the survey without satisfying at least three of the above five criteria. Table I shows their incidence in the series. Fever, as specified by Kean, was an inconstant finding. An oral temperature of 99° F or lower, throughout the first three days in hospital, was found in 73 cases (29 per cent.); in 69 of these patients the length of history was recorded, and 31 had been ill for longer than 28 days, a fact which suggests that the period of fever in hepatic amoebiasis is sometimes circumscribed. Table I shows that in 136 (54 per cent.) of the 250 cases pus in the liver was demonstrated by aspiration or by rupture, while the remaining 114 (46 per cent.) could be termed 'hepatitis' on Kean's classification. Of these 114, however, 88 showed radiological evidence suggestive of subdiaphragmatic disease. We feel that this finding suggests the probable presence of an amoebic liver abscess. Excluding patients in whom pus was demonstrated and those with radiological abnormalities, there remained a small group (26 cases) with the three criteria of a tender hepatomegaly, response to therapy, and suggestive haematology. It was this group of patients who could conceivably have been diagnosed as 'amoebic hepatitis'.

We shall now examine the five clinical criteria adopted for diagnosing the presence of hepatic reaction to the invasion by vegetative forms of the *Endamoeba histolytica*.

I. *The phenomenon of a tender enlarged liver*

Enlargement of the liver suggests one or more of the following lesions:

(1) A localized (single or multiple) expansive lesion within the substance of the liver (for example, abscess or neoplasm);
(2) A diffuse increase in the mass of either the parenchyma or the stroma, or both (for example, virus hepatitis);
(3) Prolonged biliary obstruction with diffuse dilatation of the bile-ducts;
(4) An engorgement of the vascular channels, with or without oedema of the liver cells or stroma.

We feel that this last feature has not received sufficient clinical attention in accounting for hepatic enlargement generally, and particularly in the study of amoebic liver disease. Child (1954) has reviewed comprehensively the modern concepts of the hepatic circulation. There are now strong grounds for suspecting vascular engorgement of the liver as a cause of its enlargement in conditions other than congestive cardiac failure. It is clear that the smooth muscle in the walls of the complex ramifications of the hepatic vasculature is sensitive to a variety of stimuli. Adrenaline, histamine, and hypoxia have been shown experimentally to produce profound alterations in the circulatory patterns of the liver. For example, Maegraith (1951), using the perfusion technique on dogs, showed in his experiments different reactions to adrenaline depending on whether the oxygen supply of the liver was maintained or not. He concluded that even temporary lack of oxygen resulted in spasm of the hepatic veins, with the impounding of hypoxic blood. Histamine causes in dogs and monkeys a marked swelling of the liver due to obstruction to venous outflow. Prichard (1951), from her angiographic studies of the portal circulation in animals, suggested that 'the intrahepatic vessels which transmit the portal venous blood-flow are controlled by a neuro-vascular mechanism'. In an attempt to devise a reliable radiological technique for the localization of a variety of hepatic lesions, Dr. D. Brink of this hospital has been injecting, by the retrograde route, contrast medium into the hepatic vein (usually the right). In patients with undoubted amoebic abscesses of the liver, it was found that not only did the main branches of the hepatic vein appear widely dilated, but also there seemed to be an undue patency of anastomotic channels between the various arborizations. This change was not found in non-amoebic cases. Secondly, in two patients (both with abscesses) it was found that the first injection of dye produced maximal filling of the fine tributaries, whereas subsequent injections failed to do so. An example of this reaction is clearly shown in Plate 41, Fig. 4. Bauer, Dale, Poulsson, and Richards (1932), in their experiments on dogs, showed a sphincter mechanism at the caval ostia of the hepatic veins, but our illustration suggests that a spasm even of the smaller venous tributaries within the hepatic substance has been produced by the first injection of dye. It has been found in the course of the present study that in the case of abscesses, if aspiration be stopped before complete drainage is achieved (as shown by the radiological demonstration of an air-fluid level after the instillation of air), and the liver edge be

subsequently observed, it is common for shrinkage of the liver to be greater than could be accounted for by the volume of pus removed. For example, one patient, whose liver margin extended five finger-breadths below the costal margin, had 250 ml. of pus aspirated and 50 ml. of air instilled. The edge of the liver was noted the following day to be only one finger-breadth below the costal margin. It was much less tender. A reasonable explanation of such findings would be the reversal of a congestive intrahepatic process, following even partial decompression of an abscess. The mechanism of such a process, if not that of direct pressure on large venous tributaries, could conceivably be of reflex neurovascular origin.

TABLE II

Degree of Enlargement of the Liver in 240 Cases of Amoebic Liver Disease

Degree of enlargement	*Number of cases*	*Primarily right lobe*	*Primarily left lobe*
Not palpable	27*	22	5
1–2 finger-breadths	108	94	14
3–4 finger-breadths	78	66	12
Gross	27	18	9
Total	240	200	40

* In 26 of these 27 cases there was radiological evidence of elevation of the diaphragm. In the remaining case 80 ml. of 'anchovy' pus were aspirated from the right lobe of the liver, suggesting that any enlargement present was in the horizontal plane. Pus was aspirated from 21 patients in this group, and in a further patient rupture occurred into a bronchus, with expectoration of 'anchovy' pus.

The liver may enlarge upwards or downwards. It may also enlarge in the horizontal plane. Whereas the former two dimensions are measurable by radiology and clinical palpation respectively, horizontal enlargement can be assessed only in the case of gross hepatomegaly. In the latter circumstance an undue prominence of the costal margin is a feature of gross enlargement. The findings recorded in Table II refer to downward enlargement of the liver, its margin being palpated in the right mid-clavicular line during quiet respiration, and in the mid-line below the xiphisternum.

Tenderness of the liver suggests a localized or generalized stretching or inflammation of the capsule, it being established that liver tissue itself is insensitive to pain. In the present study it was found that, when an enlarged liver was tender, the enlargement was usually rapid and progressive. Tenderness appeared to wane once enlargement was no longer progressive, or at least not rapidly so. This finding is borne out by the fact that patients with a short history of hepatic pain usually showed a greater degree of tenderness than those with a longer history (Table IV). Three aspects of hepatic tenderness were examined:

(1) 'Liver tenderness', of the palpable liver margin;
(2) 'Percussion tenderness', in relation to light percussion over the lower chest wall with the finger-tips of one hand;
(3) 'Intercostal tenderness', the reaction to intercostal palpation.

The degree of hepatic tenderness was graded in four categories for each of the preceding methods of examination:

(1) *Grade O–I.* The patient either was not tender, or had to be questioned specifically as to tenderness;
(2) *Grade I.* Moderate tenderness, in which the patient winced on gentle palpation or percussion;
(3) *Grade II.* Severe tenderness, in which the patient moved away from the examining hand;
(4) *Grade III.* Very severe tenderness, in which the patient restrained the examining hand before it reached the affected area.

TABLE III

Percentage Incidence and Grades of Tenderness Elicited in 250 Cases of Amoebic Liver Disease

Tenderness	*Grade O–I*	*Grade I*	*Grade II*	*Grade III*
Liver edge . . .	10·4	37·2	45·2	7·2
Percussion . . .	22·4	37·2	34·8	5·6
Intercostal . . .	24·4	32·4	37·6	5·6

TABLE IV

Degree of Maximum Tenderness related to Length of History in 240 Cases of Hepatic Amoebiasis

(Maximum tenderness elicited by palpation, percussion, and intercostal palpation)

Maximum degree of tenderness	*Percentage with length of history*			*Number of cases*
	Under 7 days	*8 to 28 days*	*Over 28 days*	
Grade O–I . . .	0	26·7	73·3	15
Grade I . . .	29·1	35·9	35·9	79
Grade II . . .	40·3	40·3	19·4	119
Grade III . . .	48·1	33·3	18·6	27
Number of cases . .	84	89	67	240

The incidence and grades of tenderness found by the three methods of examination are summarized in Table III. It is evident that liver-edge tenderness was found more commonly than percussion or intercostal tenderness, but the fact must be stressed that tenderness of the liver may be missed if sought only through abdominal palpation. This was particularly noticeable in patients in whom the liver margin was not palpable, yet appreciable percussion and intercostal tenderness was elicited. The relationship of maximal tenderness of the liver (however elicited) to the duration of symptoms is shown in Table IV. It was also found that of 18 patients with palpable livers in whom liver-edge tenderness was minimal or absent, 13 gave a history of hepatic pain of more than 28 days' duration, and none were ill for less than a week. Of the 18 patients with very severe tenderness, eight gave a history shorter than a week. It was found that the more generalized the pain and tenderness, the greater was the likelihood of finding pus on aspiration. This was contrary to what would be expected if one assumed that the lesion underlying the clinical syndrome preceding abscess formation was 'amoebic hepatitis'—that is, a diffuse lesion.

The following points emerge from this examination of *the phenomenon of a tender, enlarged liver*:

1. Experimental evidence in animals, as well as evidence from the present study, suggests that circulatory factors may play an important role in contributing to the production of both hepatomegaly and hepatic tenderness in amoebic liver disease.

2. The tenderness in hepatic amoebiasis may be very intense compared with that encountered in other causes of hepatomegaly.

3. For the hepatomegaly to be associated with appreciable tenderness (grades I to III), the enlargement had to be rapidly progressive, the stage of the pathological process thus assuming importance in determining the intensity of tenderness.

II. *Response to specific therapy*

Apart from the finding of a tender enlarged liver, response to specific therapy was the only criterion consistently present in the diagnosis of amoebic liver disease in the present analysis. Death took place in 16 (6·4 per cent.) of the 250 cases, in 11 instances from complications. Two of these deaths occurred in patients who did not receive specific therapy because of mistaken diagnosis. The other 14 patients all showed some response, before death, according to the criteria specified below.

Therapy. Specific therapy, apart from active procedures such as aspiration and surgical drainage, entailed the use of emetine, chloroquine, and antibiotics. The schedules recommended by Wilmot (1956) were closely followed: a 10-day course of emetine (one grain daily) together with, or followed by, a three weeks' course of chloroquine diphosphate (initial dose of 1 g. for two days, followed by 0·5 g. daily). The initial dose was reduced later to 0·75 g., because it was found that occasionally vomiting was induced by the larger dose. Antibiotic drugs were reserved for the complicated cases, particularly those involving rupture into neighbouring viscera, as well as cases of secondary infection, the appropriate antibiotic being given according to sensitivity tests.

Response. The response was considered 'rapid' if pain, tenderness, and fever were relieved within six days, and if further aspiration was not needed during this period; otherwise the response was classed as 'slow'. Of the 234 patients who survived their illness, 154 showed a rapid response, and 80 showed a slow response. The patients in the latter group had undisputed abscesses, pus being demonstrated in all cases. Among the group showing a rapid response, pus was demonstrated by aspiration or rupture in 40 cases (26 per cent. of the group). These findings suggest that when pus is abundant a slow response to specific therapy, with or without aspiration, can be expected. Several patients had obvious abscesses (visible, localized, fluctuant swellings lying superficially). These abscesses were treated with emetine, and aspiration was delayed. If the abscess was of moderate size, it commonly would disappear, making aspiration unnecessary. Experience showed that early aspiration in such cases could produce as much as 50 ml. of pus from the swelling. Wilmot (1949) drew attention

to the possibility of abscesses disappearing on emetine therapy alone. He quoted James (1946) as suggesting that the size of the abscess determined whether or not the lesion would resolve without aspiration. Ochsner and DeBakey (1943) stated that 'even large abscesses may completely disappear under emetine therapy alone'. It is convenient to differentiate abscess from 'hepatitis' by the demonstration of pus. It must be emphasized, however, that an abscess can resolve without aspiration. It is then difficult to assume that cases diagnosed as non-suppurative amoebic liver disease were not in fact instances of small deep-seated abscesses which resolved on therapy. The response in such cases is usually rapid and gratifying. We contend that the dramatic change thus achieved can be adequately explained only if we accept the hypothesis that there has been a reversal of hepatic congestion.

TABLE V

Degree of Anaemia in 227 Cases of Hepatic Amoebiasis

	No anaemia	*Moderate*	*Severe*
Haemoglobin (g./100 ml.)	Over 12	9–12	Under 9
Number of cases	119	84	24
Percentage	52·4	37	10·6

TABLE VI

Degree of Anaemia related to Length of History in 220 Cases of Hepatic Amoebiasis

	Percentage of patients with history			*Total number of cases*
	Under 7 days	*8–28 days*	*Over 28 days*	
No anaemia	53·5	34·2	12·3	114
Moderate	23·2	39·0	37·8	82
Severe	4·2	20·8	75·0	24

III. *Haematological and laboratory findings*

Erythrocytes. Anaemia (particularly the 'iron-deficient' type) is rarely seen in male Africans in this hospital. This rarity may be due to the high incidence of siderosis in the Durban African (Gillman, 1957; Wainwright, 1957; Gillman, Lamont, Hathorn, and Canham, 1957). When we find anaemia in male Africans in our unit, it is most commonly associated with hepatic amoebiasis or scurvy, the former being by far the more frequent. In the present study one patient had a mean corpuscular haemoglobin concentration of 29 per cent., which was the lowest recorded in the whole series. Anaemia in amoebic liver disease is usually of the normocytic, normochromic type, mild anisocytosis and polychromasia being the commonest abnormalities detected in the film. Table V shows the haemoglobin range in 227 cases in which the findings were recorded. Table VI shows the relationship between the degree of anaemia and the length of history in 220 cases in which the findings were recorded. From Table VI it will be seen that the degree of anaemia bears a striking relationship to the duration of the disease, the anaemia being more common in cases with long histories.

The lowest haemoglobin level recorded was 4·2 g. per 100 ml. (packed cell volume 13 per cent., mean corpuscular haemoglobin concentration 32 per cent.). In this unit the finding of anaemia associated with a tender enlarged liver is regarded as strong evidence that we are dealing with hepatic suppuration. It is remarkable how rapidly the blood picture returns to normal once adequate therapy has been instituted in cases as extreme as that just referred to. In patients in whom the blood picture was examined repeatedly, it was rare for the haemoglobin not to have returned to normal within three weeks.

TABLE VII

Leucocyte Counts per cu. mm. in 230 cases of Hepatic Amoebiasis

	Under 9,000	*9,000–15,000*	*15,000–25,000*	*Over 25,000*
Number of cases . .	42	80	86	22
Percentage . . .	18·3	34·8	37·4	9·5

TABLE VIII

Leucocyte Counts related to Duration of Illness in 222 Cases of Hepatic Amoebiasis

	Percentage of patients with history			*Total number of cases*
Leucocytes/cu. mm.	*Under 7 days*	*8–28 days*	*Over 28 days*	
Under 9,000 . . .	28·5	28·5	43·0	42
9,000–15,000 . .	34·2	42·1	23·7	76
15,000–25,000 . .	41·5	30·5	28·0	82
Over 25,000 . . .	36·3	45·4	18·3	22

Occasional cases of profound anaemia encountered in the present study provided evidence suggesting a haemolytic process (slight elevation of the serum-bilirubin level, polychromasia, anisocytosis, and reticulocytosis). Laser (1951) described a haemolytic substance extractable from foetal and adult guinea-pig liver, and showed the activity of this substance to be inhibited by certain factors in plasma and serum (albumin, globulin, calcium, cholesterol, and lecithin). It is hoped to subject a further group of patients to more careful haematological examination, to investigate the possibility of a haemolytic process being the basis of the profound anaemia sometimes found in hepatic amoebiasis, particularly in cases with large abscesses. The rapid return of the haemoglobin levels to normal in cases with profound anaemia could thus be explained by the combination of sudden cessation of haemolysis with the release of the bone-marrow from the toxic action of either amoebae or some derivative of the host's necrotic liver tissue.

The leucocytes were examined in 230 cases; the findings are recorded in Table VII. Table VIII shows the relationship between the leucocyte count and the duration of history in 222 cases in whom both these findings were recorded. Analysis of Tables VII and VIII reveals the following facts:

1. Fifty-three per cent. of the patients had white-cell counts below 15,000 per cu. mm., and 47 per cent. above 15,000 per cu. mm. In 9·5 per cent. the leucocytosis was over 25,000 per cu. mm. McFadzean, Chang, and Wong (1953) and

Manson-Bahr and Willoughby (1929) referred to the lack of marked elevation of the leucocyte count as being a feature of amoebic liver abscess. The former authors stated that 'the marked elevation of the leucocyte count helps to distinguish pyogenic (liver) abscess from amoebic abscess'. In all our 11 patients who died and who were subjected to autopsy the presence of amoebic liver abscess was confirmed. Four of these patients had leucocyte counts over 25,000 per cu. mm., one having a count of 45,000 per cu. mm., aerobic and anaerobic culture of the pus from the latter patient being sterile. The conclusion based on the material seen in this series is that the level of the leucocyte count is not a reliable criterion for distinguishing between pyogenic and amoebic liver abscess.

2. The relationship of the leucocyte count to the duration of the illness indicates that the longer the history, the less likelihood there is of a markedly elevated white-cell count, and the greater the chance of the count being normal. Even, however, when the numbers of circulating leucocytes were within normal limits, the differential count often revealed a polymorphonuclear preponderance with 'toxic' changes in the cells. On the other hand, the shorter the history, the greater is the likelihood of the white-cell count being appreciably elevated.

Thus correlation between degree of anaemia, leucocytosis, and duration of illness, reveals that patients with a short history tend to show no anaemia but appreciable leucocytosis, whereas those with a long history show appreciable anaemia with less marked leucocytosis.

Biochemical tests of liver function. The examinations conducted included serum-bilirubin levels, alkaline phosphatase, zinc turbidity, plasma-proteins, and cephalin-cholesterol estimations. One of Kean's (1955) criteria for the diagnosis of the syndrome 'amoebic hepatitis' was laboratory evidence of disturbed hepatic function. In this hospital African male patients regularly show abnormal results of liver function tests, whether they are suffering from hepatic amoebiasis or not. The majority of the tests enumerated above were carried out in 75 per cent. of the 250 cases in the present survey.

1. *Serum-bilirubin* was found to be over 0·8 mg. per 100 ml. in 19 out of 187 cases. The mean in these 19 cases was 3·2 mg., and the range 0·9 mg. to 11·3 mg., per 100 ml. Six of these 19 patients died. Autopsy was performed in four cases. In each case large abscesses were found, and it was presumed that these were at least in part responsible for the jaundice, perhaps by occluding the bile-ducts of one or more lobes. As there were only 16 deaths in the entire series, it appears that increased serum-bilirubin in amoebic liver disease should be viewed as a serious portent. A leucocytosis of over 20,000 per cu. mm. was found in 10 patients with elevated serum-bilirubin levels. Some of the highest leucocyte counts of the whole series were found in this group, for example, 48,000, 45,000, 39,000, 33,000, 27,000, and 24,000 per cu. mm.

2. *Serum alkaline phosphatase and zinc turbidity.* The alkaline phosphatase was within normal limits in 136 (72 per cent.) of 189 cases examined. Levels above 14 King-Armstrong units were found in 53 cases, with the mean 22 units

and the range extending from 15 to 46 units. Zinc turbidity was recorded in 192 cases and was found to be normal in 106. The 'normal' range in this series was up to 14 units, which is probably high. Thus 85 cases (44·8 per cent.) showed distinct elevation, the mean being 19·5 units and the range 15 to 40. Thirty-one patients showed concomitant elevation of alkaline phosphatase and zinc turbidity levels. In addition, eight of these patients showed elevation of serum-bilirubin levels.

3. *Plasma-proteins.* Only one patient out of 191 examined showed an albumin-globulin ratio which was greater than unity. Reversal of this ratio is common in this hospital, and would suggest that amoebic infestation of the liver develops in patients in whom functional derangement of the liver, at least, is already present. Evidence has also been acquired of a high incidence of underlying hepatic disorder in male Africans in Durban (Gillman, Lamont, Hathorn, and Canham, 1957; Wainwright, 1957). In patients in whom repeated plasma-protein estimations were possible, improvement was the rule. This finding has been noted by Powell (1957) in this hospital.

It appears from the above findings that liver function tests are of no help in the specific diagnosis of hepatic amoebiasis, but may be of some value in assessing the outcome of the disease.

IV. *Radiological findings*

Owing to the need for a rapid turnover of patients in the wards and in the radiology department, X-ray screening of diaphragmatic movement in amoebic liver disease is not feasible as a routine diagnostic procedure in this hospital. In practice, however, it has been found that the information given by a radiograph provided adequate diagnostic confirmation in a high proportion of cases, abnormalities being detected in 84 per cent. of patients subjected to X-ray examination. The radiological findings are shown in Table IX.

Absence of radiological abnormality in hepatic amoebiasis suggests one or more of the following possibilities:

1. That the hepatic enlargement is primarily an intraperitoneal encroachment. In four of the 40 patients with negative findings rupture occurred into the peritoneal cavity. In a further 19 the liver showed marked enlargement downwards on clinical examination. Of these 23 patients who had obvious downward enlargement of the liver, no less than seven had left-lobe abscesses. It appears that, owing to its anatomical relationships, an abscess of the left lobe does not become radiologically evident until it is about to rupture into the thoracic cage. This is well demonstrated in Plate 43, Fig. 7. Of two further cases, one yielded 80 ml. of pus on aspiration, and the other 470 ml. The latter case came to autopsy, and the abscess cavity was found to communicate with the lumen of the hepatic flexure of the colon; the liver was distinctly enlarged. These two cases suggest that enlargement took place in the horizontal plane.

2. That there is a hepatic lesion of small dimensions. Of the remaining 15 patients, in whom the X-ray findings were negative and there was no gross peritoneal encroachment, the size of the liver was specifically noted in 14, and

none showed an easily appreciable enlargement (more than two finger-breadths). In two of these cases a small amount of pus (10 ml.) was aspirated.

Positive radiological findings were observed in 202 cases (84 per cent.). One hundred and sixty-eight showed elevation of the diaphragm. Thirty-three cases,

TABLE IX

Radiological Findings in 242 Cases of Hepatic Amoebiasis

Findings		*Number of cases*	*Percentage*
Negative		40	16·5
Elevation of diaphragm	Right	156	64·4
	Left	12	5·0
Pleural reaction:			
With little or no effusion	Right	60	24·8
	Left	5	2·1
With large effusion	Right	17*	7·0
	Left	2	0·8
Linear atelectasis	Right	30	12·4
	Left	4	1·6
Lower lobe consolidation:			
'Pneumonitis'	Right	59	24·8
	Left	6	2·5
Lobar	Right	6†	2·5
	Left	3	1·2
Lung abscess	Right	7‡	2·9
	Left	4	1·6
Pericardial involvement		7	2·9

* Includes nine cases in which pus was tracking up the greater fissure (Plate 42, Fig. 5).

† Although an opacity of lobar distribution was recorded, and no abscess visualized radiologically, abscess formation was suspected on clinical grounds ('anchovy' pus expectorated).

‡ Includes a large subdiaphragmatic amoebic abscess in which an air-fluid level was seen, yet no aspiration had been performed (Plate 42, Fig. 6).

in which such elevation was not seen, showed varying X-ray evidence of supra-diaphragmatic lesions. In a further case (see below) a radiograph showed a subdiaphragmatic abscess only after aspiration. The findings in these 34 cases were as follows:

1. Patchy pneumonitis at the right base (15 cases). Six of these cases yielded pus on liver aspiration.

2. Right basal pleural reaction (14 cases). Seven yielded pus from the liver, and in a further two pus was obtained from the pleural cavity.

3. Basal linear atelectasis only (two cases). One of these two patients died (he had an acute psychosis associated with pellagra, and the abscess was diagnosed at autopsy). The other had an acutely tender enlarged liver, a leucocytosis, and a history of recent amoebic dysentery with positive findings in the stools, and he showed a response to specific therapy.

4. Pericardial effusion (two cases). Amoebic pus was demonstrated in the pericardium in both cases (*post mortem* in one case).

5. One patient, whose original radiograph was negative, had 50 ml. of pus

aspirated from the liver, and air instilled. The subsequent radiograph revealed the abscess cavity.

V. *The demonstration of pus, either by aspiration or by rupture*

A. *Rupture of abscesses.* Fig. 1 shows the incidence of rupture, which occurred in 44 cases.

Downward rupture. In 11 cases rupture occurred downwards, in one case into the hepatic flexure of the colon, and in 10 into the peritoneal cavity. One of these patients died, the diagnosis being confirmed at autopsy. In five others the diagnosis was confirmed at laparotomy.

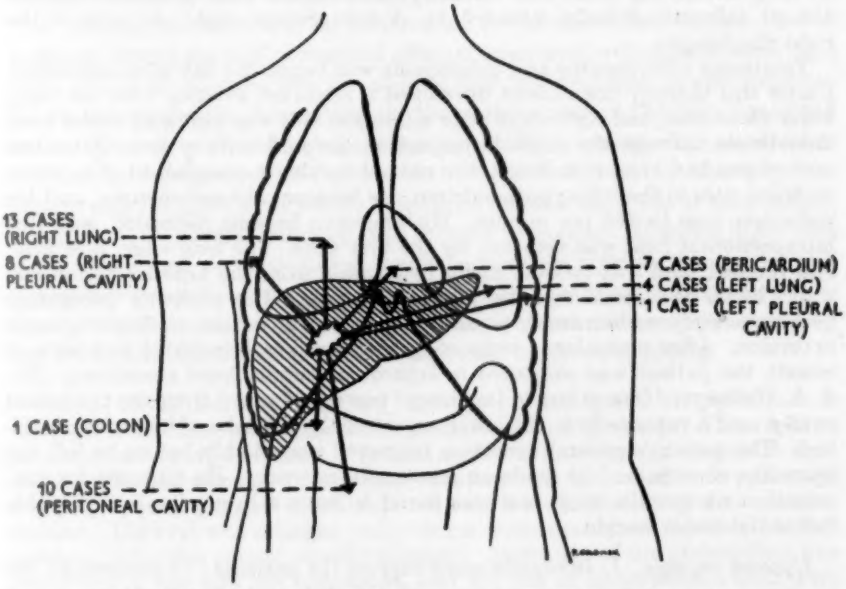

FIG. 1. Direction of rupture in 44 cases of amoebic liver abscess.

Features of intraperitoneal rupture.

1. Sudden acute abdominal pain, with clinical evidence of traumatic shock.

2. A short-lived peritonism, soon followed by clinically demonstrable free fluid. With gross distension, the abdominal wall was often flaccid, and there was often cardio-respiratory embarrassment.

3. Recession of the liver edge, which became firmer to the touch and amenable to ballottement.

4. Provided the patient survives the initial effects of the rupture, the prognosis seems favourable and the after-effects slight. It is surprising how innocuous may be the long-term results of amoebic liver pus within the peritoneal cavity.

One case of intraperitoneal rupture of an amoebic liver abscess is worth description:

An African man aged 24 years gave a three months' history of painful abdominal swelling and loss of weight. He was severely emaciated, and his ankles were oedematous. The liver edge was palpable well below the umbilicus, and was smooth and rounded, and only moderately tender. Initially the diagnosis of primary carcinoma was made. This condition, together with primary lung disease, constitutes the main diagnostic problem of amoebic liver disease in Durban Africans. The laboratory findings were: haemoglobin 8 g. per 100 ml., packed cell volume 36 per cent., and mean corpuscular haemoglobin concentration 30 per cent.; white cells 10,000 per cu. mm. (polymorphs 59 per cent., lymphocytes 30 per cent., monocytes 11 per cent.); serum alkaline phosphatase 19 King-Armstrong units, zinc turbidity 20 units, and total proteins 7·8 g. per 100 ml. (albumin-globulin ratio 0·5:1). X-rays showed slight elevation of the right diaphragm.

Treatment with emetine and chloroquine was begun the day after admission. Under this therapy the patient developed a fluctuant swelling over the right lower chest wall, and eight days after admission this was aspirated under local anaesthesia through the ninth interspace in the mid-axillary line. After one pint of pus had been withdrawn, the patient suddenly complained of a severe stabbing pain in the left hypochondrium. He became cold and clammy, and his pulse-rate rose to 168 per minute. His abdomen became distended, and free intraperitoneal fluid was detected for the first time. The liver edge, now firm, had receded, and had become easily ballottable from the anterior abdominal wall. Little abdominal rigidity was encountered. The patient's respiration became acutely embarrassed, possibly owing to restriction of diaphragmatic excursion. After preliminary supporting therapy (which included two pints of blood), the patient was subjected to laparotomy under local anaesthesia (Dr. J. A. Hofmeyr). One gallon of 'anchovy' pus was drained from the peritoneal cavity, and a rupture from the lower aspect of the left lobe of liver was identified. The patient's general condition improved remarkably before he left the operating theatre, and he made an uneventful recovery. He returned for examination six months later, and was found to have a liver edge just palpable below the costal margin.

Upward rupture. 1. *Intrapulmonary rupture* (17 patients; 16 recovered). In seventeen cases rupture occurred into the lung (the right lung in 13 cases, and the left in four), and the patient coughed up amoebic pus. Six patients had radiologically demonstrable lung abscesses as well as involvement of the diaphragm, pleura, and lung parenchyma. One of these patients coughed up bile in his sputum, but eventually recovered completely. Eight patients had involvement of diaphragm, pleura, and lung, without demonstrable abscess. Included among these was the only fatal case of intrapulmonary rupture: the patient expectorated bile, and died after becoming progressively more cachectic (Plate 42, Fig. 5). Two patients had patchy pneumonitis only, involving the right lower lobe of lung. One patient (see Plate 42, Fig. 6) had a large abscess, with an air-fluid level, under a markedly elevated right diaphragm. At no stage was pus aspirated, the conclusion being that a spontaneous broncho-hepatic fistula had developed. He recovered completely, draining his abscess through this fistula.

2. *Intrapleural rupture* (nine cases; one death). In nine cases the abscess ruptured into the pleural cavities (eight times on the right and once on the left side). There was one fatal case, due to acute mediastinal displacement. The pleural cavity was aspirated shortly after the intrapleural rupture in this case, and pus exuded under pressure from the needle. The one case in which rupture took place into the left pleural cavity presented special features: the pus tracked anterior to the pericardium, and two pints of 'anchovy' pus were aspirated via the seventh interspace in the mid-clavicular line, after aspirations in the mid-axillary and scapular lines had proved negative. (Fig. 7 (Plate 43) shows the X-ray pictures before and after rupture in this case.) In all cases the culture of the pus was sterile, and, apart from the one death described, response to specific therapy was complete though slow.

3. *Amoebic involvement of the pericardium* (seven cases; five deaths). Seven patients showed signs of pericardial effusion associated with liver abscess; five died, and in all of these five the abscess had ruptured into the pericardium. There are apparently three phases in the pathogenesis of the fully developed lesion. There is an initial 'sympathetic' or slightly purulent effusion, which is followed by intrapericardial rupture of the hepatic abscess. At this stage the patient may die (see Case 1 below). The third phase is the phase of constriction, which may take several weeks or even months to develop. It seems likely that a carefully timed pericardectomy would be the only possible therapy for this apparently inevitable sequel. The first two phases are clearly demonstrated in Case 1. For the notes of this patient, the only one not examined personally by one of the authors (N. M. L.), we are indebted to Dr. S. Goldberg.

Case 1. An African man, aged 25 years, gave a five weeks' history of pain in the right lower chest and epigastrium, associated with dyspnoea. There was no previous history of dysentery. He had no fever, but was cachectic. On examination he had signs of a pericardial effusion, with distended neck veins, and a typical pulsus paradoxus; X-rays showed a characteristic globular heart-shadow. His liver was enlarged to five finger-breadths and moderately tender; right and left lobes seemed equally enlarged. Aspiration of the pericardium was performed in the fifth left interspace, and 500 ml. of blood-stained fluid were removed. The report on this fluid was: 'pus cells, lymphocytes, and erythrocytes; protein 5·5 g. per cent.'. The patient was regarded as suffering from tuberculous pericarditis, and was treated with streptomycin and isoniazid. After an initial response, he rapidly deteriorated, and died 13 days after admission. At autopsy a large amoebic liver abscess in the left lobe was found to have ruptured into the pericardium.

Case 2. This patient illustrates the first phase of pericardial involvement. He was 25 years old, and on admission on 3.4.57 gave a two months' history of pain in the right lower chest and epigastrium, worse at night, referred to the shoulder, and associated with cough, dyspnoea, fever, and chills. He gave a history of dysentery in 1948. Examination revealed slight fever (99·6° F.) in an acutely dyspnoeic, cachectic young African (weight 108 lb.). The initial impression was one of acute cardiac failure with pericardial effusion. The patient was orthopnoeic, his neck veins were distended, and the liver was five finger-breadths enlarged and very slightly tender. The pulse-rate was 172 per minute.

A pericardial friction was audible, and persisted for three days. The electrocardiogram on the day of admission is shown in Fig. 2. There was palpable epigastric pulsation.

Despite the rather tenuous evidence of a possible underlying amoebic abscess, aspiration of the left lobe of the liver (in the epigastrium) was undertaken. Pus (50 ml.) was withdrawn, and 15 ml. of air instilled, with immediate relief to the patient. On two subsequent occasions 500 ml. and 1,000 ml. of pus were

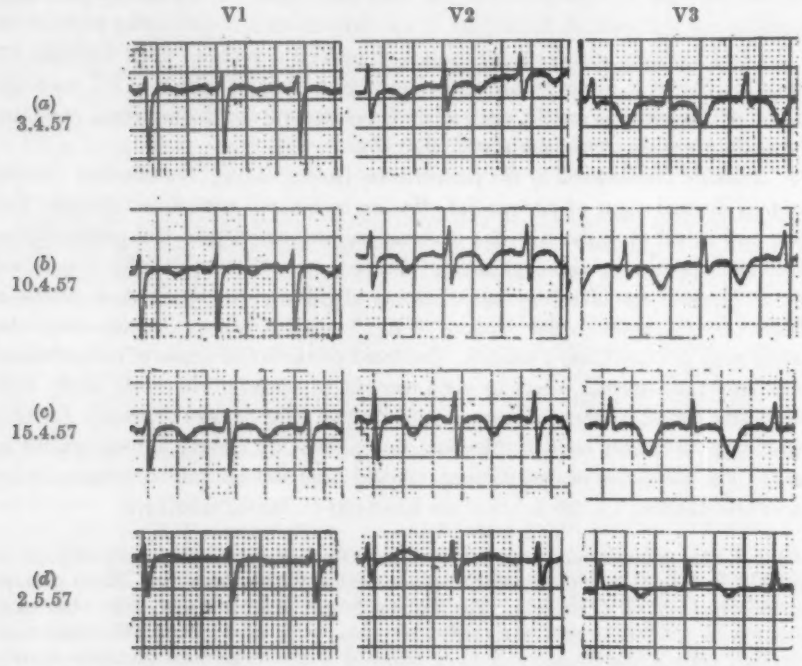

FIG. 2. Case 2. Electrocardiogram (chest leads) (*a*) on the day of admission, (*b*) one week later, (*c*) a further five days later, and (*d*) one month after admission.

aspirated, and air instilled in the abscess cavity (see Plate 43, Fig. 8). Laboratory findings were: haemoglobin 9·6 g. per 100 ml., packed cell volume 30 per cent., and mean corpuscular haemoglobin concentration 32 per cent.; white cells 10,000 per cu. mm.; serum alkaline phosphatase 13 King-Armstrong units, zinc turbidity 26 units, total proteins 7·4 g. per 100 ml. (albumin-globulin ratio 0·3:1). He was treated initially with chloroquine and oxytetracycline, and subsequently with 10 days of emetine ($\frac{1}{2}$ grain), followed by a further course of 10 grains of emetine after a free interval of two weeks.

The clinical, electrocardiographic and radiological evidence suggested that there was a localized pericarditis with 'sympathetic' effusion, and that rupture was imminent. He made an uneventful recovery, and subsequent examination two months later showed no evidence of clinical or radiological abnormality.

Case 3. This patient, aged 25 years, gave a three days' history of pain in the left epigastrium and left lower chest, referred to the left shoulder, worse at night, and associated with fever and chills. Three days after admission he

became suddenly distressed, and the left lobe of the liver was explored with a needle, but only 5 ml. of thick pus could be withdrawn. He was subjected to laparotomy on the same day, and an amoebic abscess in the left lobe of the liver, tracking into the pericardium, was drained. The electrocardiogram, which is shown in Fig. 3, was recorded before operation. The patient was greatly relieved by the operation, but slowly redeveloped cardiac tamponade. Despite further efforts at drainage of the pericardium he died six weeks after admission. At autopsy there was minimal fluid in the pericardial sac, and an organizing pericarditis was found.

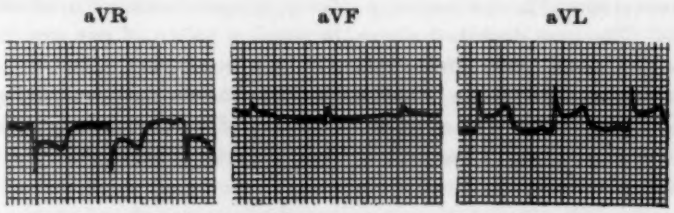

FIG. 3. Case 3. Electrocardiogram (leads aVR, aVF, and aVL) taken shortly after intrapicardial rupture. A subsequent electrocardiogram showed changes similar to those seen in Fig. 2.

Case 4. This patient was admitted twice. On the first occasion he weighed 92 lb., although he was an adult, and had an uncomplicated amoebic abscess of the right lobe of the liver, from which 560 ml. of pus were aspirated. Eight months after discharge he was readmitted with a pericardial effusion. The X-ray picture (Plate 44, Fig. 9), taken after a total of 2,500 ml. had been aspirated from the pericardium on separate occasions, demonstrates the thickened pericardial wall. He was eventually subjected to surgery, but died two months after admission from constrictive pericarditis.

Case 5. The X-ray picture (Plate 44, Fig. 10*a*) was taken on admission when the patient was critically ill. Fig. 10*b* shows the radiograph after surgical drainage had been performed (Mr. E. M. Barker). Before surgery four pints of yellow pus were aspirated from the pericardium via several approaches. Difficulty was encountered because the pus was very viscid and appeared to have many sloughs and fibrin clots in its substance. The abscess in the left lobe of the liver was opened under general anaesthesia. A ragged three-inch track in the roof of the abscess was found to communicate with the pericardial sac. A gallon of pus, containing innumerable sloughs, was removed, and a catheter was left *in situ* as a drain. Pus was drained daily, and oxytetracycline and emetine were instilled through the catheter. Despite this therapy the patient died three months after admission from the inevitable cardiac tamponade attendant on a progressively constrictive pericarditis.

Cases 6 and *7.* These were respectively a 'sympathetic' effusion, with recovery, and a frank rupture; in the latter case the patient died from a constrictive pericarditis, which was confirmed at autopsy.

B. *Aspiration.* In 106 cases pus was aspirated from the liver. In 14 of these cases the abscess also subsequently ruptured into adjacent viscera or serous cavities. Three types of pus were aspirated: (1) frankly purulent (36 cases); (2) 'anchovy' pus (43 cases); (3) blood mixed with pus (27 cases). The first type

needs no qualification. The distinctive feature of the second type was the presence of apparently necrotic liver tissue, giving the 'anchovy' appearance. The nature of the pus in the third type was established by microscopic examination. In 13 of the 106 cases (12 per cent.) bacteria were isolated by aerobic or anaerobic culture.

Eighty patients underwent aspiration once only, and 26 more than once. Contrary to the findings of McFadzean, Chang, and Wong (1953), pain was not experienced during the course of aspiration, even when as much as two litres of pus were removed in one operation. The only reaction shown in all our cases was relief. The case described above, in which a gallon of pus was removed from the peritoneal cavity after rupture of an abscess, emphasizes one hazard to be guarded against: *in the presence of a large abscess, the possibility of additional abscesses must not be ignored.* The emptying of one abscess may apparently facilitate the stretching of the wall of a neighbouring abscess, with the danger of provoking rupture.

Causes of Death (16 cases)

1. *Eleven patients subjected to autopsy.* (1) Five patients died of amoebic pericarditis after rupture of the abscess into the pericardium. These five included one of the cases diagnosed only at autopsy, in which no specific therapy was given. (2) In the other patient who did not receive specific therapy an amoebic abscess was demonstrated at autopsy. He was admitted suffering from acute pellagra and dementia, which obscured any symptoms referable to the abscess of the liver. (3) One patient was deeply jaundiced (serum-bilirubin 11·3 mg. per 100 ml.). He developed a severe melaena two days after 250 ml. of pus had been aspirated from the right lobe of the liver. Autopsy revealed five large amoebic abscesses within the substance of the liver. In addition there was active amoebic ulceration of the caecum, from which the melaena was suspected to have arisen. Histological examination also revealed advanced hepatic siderosis and portal cirrhosis. (4) Three patients appeared to die of toxaemia. The first had a large amoebic abscess which yielded a pure culture of *Staphylococcus aureus*. In the second case the abscess communicated with the hepatic flexure of the colon, and was infected with *Bacterium coli*. The third patient had an abscess so deep-seated that it could have been reached only by exploring from a posterior approach. Repeated exploration before death failed to locate the abscess. (5) One patient died as the result of acute peritonitis following downward rupture of an abscess 'consistent with amoebic aetiology but with no amoebae found' (Dr. J. Wainwright). He was an 18-year-old youth with a three months' history of hepatic pain. Consent for operation was not forthcoming.

2. *Five patients not subjected to autopsy.* (1) One patient died after acute mediastinal displacement due to rupture of an amoebic abscess into the right pleural cavity. (2) One patient was jaundiced (serum-bilirubin 7·4 mg. per

100 ml.). He improved on specific therapy, and was transferred to a convalescent hospital, where he died; the circumstances of his death were unfortunately unobtainable. (3) Two patients are considered to have died of hepatic failure. Both became progressively more cachetic after the aspiration of large quantities of pus from the liver. One yielded three and a half litres of thin, watery pus; the other, after the removal of pus by aspiration, developed a hepato-bronchial fistula, and coughed up bile in his sputum. (4) One patient died unexpectedly the day after his admission, when an intraperitoneal 'leak' was suspected, and when 750 ml. of pus were aspirated from the right lobe of the liver.

Discussion

Ochsner and DeBakey (1943) have been instrumental to a large extent in placing our present-day concepts of hepatic amoebiasis on a sound scientific basis. Their analysis of 181 cases, published in 1943, has come to be recognized as a classic study. In this study, however, they stated: 'In the early phase of an amoebic hepatitis a balance exists between regression towards healing by scar tissue replacement and progression towards suppuration and abscess formation.' And later: 'The importance of recognizing the early development of amoebic hepatitis has been emphasized repeatedly. During this early or pre-suppurative stage, there is invasion of the liver by amoebae but the abscess formation has not yet occurred. The obvious significance of recognizing this period lies in the fact that the institution of appropriate therapy may prevent progression to abscess formation.' They also reported, however, that abscesses may disappear completely on emetine therapy alone. Careful study of the history and findings in the case which they quoted as exemplifying the pre-suppurative stage leads the present authors to suggest that Ochsner and DeBakey were not justified in diagnosing 'hepatitis' as opposed to abscess. This case can, on their facts and our criteria, justifiably be regarded as typical of an abscess (tender hepatomegaly, a leucocyte count of 24,000 per cu. mm., and a highly suggestive radiograph), but for the fact that the whole condition subsided on emetine without recourse to aspiration. That an undoubted abscess can subside on emetine therapy has repeatedly been found in the present study. On the basis of the evidence here shown we contend that the characteristic symptoms and clinical findings, as seen in Ochsner and DeBakey's case, as well as the radiological findings, are unlikely to develop until frank abscess formation has occurred.

Kean (1955) suggested that in intestinal amoebiasis the liver, acting as the venous depot of the alimentary tract, may be invaded by bacteria, debris, and other 'noxious' material. This, he supposed, may cause '. . . sufficient hepatic reaction to come to clinical attention'. We feel that Kean's hypothesis of the pathogenesis of 'amoebic hepatitis' cannot be considered adequate to account for the severe symptoms and signs usually found, especially in the total absence of supporting pathological evidence. The hepatic tenderness of infective hepatitis, for instance, is rarely comparable with that so frequent in amoebic liver disease, despite the appreciable hepatic reaction in the former.

The experimental work of Maegraith and Harinasuta (1953) on mice may be significant in clarifying the problem of the pathogenesis of hepatic amoebiasis. They found that injection of amoebae into the portal circulation usually failed to produce any hepatic lesion. If, however, intestinal amoebiasis had previously been established, a hepatic lesion could then be produced by intraportal injections of amoebae. Such lesions resembled localized infarcts, amoebae being indentifiable in the lesion. The mechanism involved would appear to be of an immunological nature. As long ago as 1927 Craig described a specific complement-fixation test for *Endamoeba histolytica* infestations, and it is significant that, given a potent antigen, the test is positive in a very high percentage of cases of hepatic amoebiasis.

We have been impressed by the number of patients with histories of less than a week's illness in whom as much as 250 ml. of pus could be aspirated from the liver. This observation suggests that the early phase of the pathological process was focal and subclinical. Only when rapid and appreciable liver-cell necrosis developed, with its attendant effects on the liver and its capsule, did the hepatic reaction become sufficient in our patients to arouse symptoms and clinical attention. In the present series three patients were encountered in whom a history was given of sudden, severe pain and swelling developing immediately after a violent movement, for example, the lifting of a heavy weight. All three were working up to the day of admission. In two of these cases aspiration was not performed, but aspiration in the third case yielded on the day of admission 30 ml. of a blood-stained fluid, which on microscopy was found to contain large numbers of pus-cells. All three patients had acutely tender, fluctuant hepatic swellings in the epigastrium, and were severely incapacitated, so that they moved cautiously in bed. Response to specific therapy, even in the absence of aspiration, was rapid. It was concluded that in all three cases a sudden haemorrhage had occurred into a 'silent' abscess or focal hepatic lesion. We therefore believe that the earliest phase of an amoebic abscess is a 'silent' focal lesion, possibly an infarct similar to that induced by Maegraith and Harinasuta in their experiments, which infarct may be single or multiple. Such focal lesions may either resolve without abscess formation, thereby escaping clinical attention, or progress acutely or gradually to frank abscess formation. Vascular factors, as well as immunological mechanisms, may be of importance in determining the ultimate course of the hepatic reaction.

There is a high incidence of helminthiasis in Africans in Durban. Of 150 patients in our series whose stools were examined, 77 per cent. were infested with worms (*Ascaris lumbricoides*, *Trichuris trichiura*, *Taenia*, or less commonly *Ankylostoma duodenale*). All these parasites can produce minimal mucosal lesions of the bowel, and it is possible that they may thereby predispose the host to hepatic amoebiasis by facilitating the entry of the *Endamoeba histolytica* into the portal circulation, although the latter parasite is known to be able to penetrate to the submucosa by its own action. One of us (N. M. L.) has been associated with a study of diseases of the liver (other than amoebiasis) as seen in this hospital (Gillman, 1957; Gillman, Hathorn, and Lamont, 1957; Gillman,

Lamont, Hathorn, and Canham, 1957). Needle biopsies have, to date, been performed on over 300 patients suffering from a variety of conditions, including cirrhosis, siderosis, and carcinoma. Among these were 29 patients in whom the diagnosis of hepatic amoebiasis was made according to the criteria detailed in the present study. Examination of serial sections from these biopsies were conducted by Professor T. Gillman. Details of the findings will be published elsewhere. For the present, however, it can be stated that, in the biopsy material from patients with hepatic amoebiasis, Professor Gillman could not detect any diffuse hepatic lesion comparable in any way with the diffuse dissociation of liver cords and other changes typical of viral hepatitis. Only small scattered microscopic foci of colliquative liver-cell necrosis were seen in biopsies from some of our patients, in all of whom pus had been demonstrated.

It has been established that there is a high incidence of hepatic disorder among male Africans in this hospital (Wainwright, 1957; Gillman, Lamont, Hathorn, and Canham, 1957). H. H. Anderson (1953) has stated: 'It is probable that the amoeba finds survival especially difficult in the healthy liver.' In view of the frequency of alimentary amoebiasis in Durban Africans, the high incidence of hepatic amoebiasis shown in the present series is not unexpected.

Conclusions

1. There is strong evidence to suggest that no pathological basis exists for the clinical entity traditionally described as 'amoebic hepatitis', and that this is therefore a misnomer.

2. It is suggested that 'amoebic hepatitis' probably represents one or more deep-seated abscesses of small dimensions, resolving on specific therapy without recourse to aspiration.

3. The five criteria which are considered to be of value in reaching the diagnosis of hepatic amoebiasis are: (1) An enlarged liver which is usually tender, at least at some stage. (2) Response to specific anti-amoebic therapy. (3) Suggestive haematological findings. (4) Suggestive radiological findings. (5) The demonstration of amoebic pus, either by aspiration or on the occurrence of spontaneous rupture into an adjacent viscus or serous cavity.

4. Hepatomegaly is a *sine qua non* in the diagnosis of amoebic liver disease, the enlargement taking place upwards, downwards, or in the horizontal plane. There is evidence to suggest that congestive vascular factors may contribute appreciably to the hepatomegaly of amoebic liver disease, in addition to the expansive effect of one or more abscesses.

5. From an analysis of the pain and tenderness associated with the condition it is concluded that the severity of the symptoms is directly related to the speed of development and progression of the abscess. An immunological basis for the rapidity of development of abscesses is suggested. The pain and tenderness in hepatic amoebiasis are usually far greater than those encountered in other conditions associated with hepatomegaly; in our experience amoebiasis is equalled

only by primary carcinoma as a cause of painful enlargement of the liver in African patients.

6. Response to specific therapy is eminently satisfactory. Despite a high incidence in our wards of cases which could be classified as 'advanced', even on admission, the death-rate was surprisingly low (6·4 per cent.) in view of the extent of hepatic destruction. This low death-rate is attributed to the fact that in this hospital there is considerable awareness of the condition because of its high incidence, and therefore minimal delay in the institution of specific therapy.

7. Our findings confirm those of Wilmot (1949) that amoebic liver abscesses can resolve on emetine or chloroquine therapy, or both, without other measures. It is suggested that such responses of frank abscesses (perhaps often undiagnosed) have been largely responsible in many cases for a clinical diagnosis of 'amoebic hepatitis' rather than abscess.

8. The haematological findings are intimately related to the duration of the hepatic abscess. Patients with a short history tend to show no anaemia, but appreciable leucocytosis, whereas those with a long history show anaemia, but less marked leucocytosis. Jaundice was usually found to be associated with a marked leucocytosis. Jaundice carries a serious prognosis; it was present in six of the 16 fatal cases. An elevated serum-bilirubin level was commonly associated with increased alkaline phosphatase, suggesting a superimposed obstructive basis for the jaundice. The differentiation of amoebic liver abscess from (non-amoebic) pyogenic abscess is not possible on the basis of the leucocyte count. The plasma-proteins were disturbed in the majority of cases, but showed appreciable improvement in cases in which follow-up was possible. No conclusion could be drawn from this disturbance, which is common in African patients, with all types of disease, admitted to this hospital (Powell, 1957; Joubert, 1957).

9. It is suggested that postero-anterior and lateral radiographs of the chest provide valuable and adequate diagnostic information of this condition, without recourse to screening. Often patients in whom such radiographs give negative information have clinically obvious intra-abdominal enlargement of the liver.

10. Rupture of hepatic abscesses into adjacent viscera or serous cavities (pleural, peritoneal, and pericardial) took place in one-third of the cases in which pus was demonstrated. By far the most serious complication is rupture of an abscess into the pericardial sac. All of the seven patients with pericardial involvement had abscesses of the left lobe of the liver. It is concluded that left-lobe abscesses should be viewed with the greatest circumspection, and the patients should be subjected to laparotomy if adequate aspiration cannot be achieved. This, in our view, constitutes the only indication of surgical intervention in uncomplicated hepatic abscesses.

11. It is believed that the earliest phase of amoebic liver disease is a focal lesion, which may be a 'silent' hepatolytic process, not evoking clinical attention until it has progressed to a larger abscess. This progression may be due to immunological mechanisms participating not only in the initial lesion but also in its progress to widespread tissue necrosis.

12. Hepatic circulatory changes may play as prominent a role as the abscesses themselves in the production of symptoms and signs, and especially of tender hepatomegaly.

We thank Dr. S. Disler, Superintendent of King Edward VIII Hospital, for permission to publish; Professor E. B. Adams and Dr. A. J. Wilmot, of the Department of Medicine, for their help and encouragement; and Dr. F. J. Davidson for access to his patients. In particular we thank Dr. D. Brink, head of the Department of Radiology, for permission to mention material from his own research project; Professor I. Gordon and his colleagues of the Department of Pathology; and Miss A. Killerby for the clinical photography. Finally we would like to acknowledge our debt of gratitude to Professor T. Gillman and Dr. M. Hathorn, of the Department of Physiology, for their invaluable advice and constructive criticism.

Summary

Two hundred and fifty patients have been examined from a clinical, radiological, and laboratory viewpoint. Five criteria have been adopted in their examination, and these are detailed. The clinical and laboratory findings showed a distinct relationship to the stage of the pathological process, whether early or advanced.

The literature has been studied, and a discrepancy is noted between the clinician's viewpoint regarding amoebic liver disease and that of the pathologist. The present study has failed to provide clinical evidence to support the concept of a diffuse lesion. We feel that the earliest clinically recognizable lesion is the stage of abscess.

Immunological and hepatic circulatory mechanisms are suggested as being of importance not only in the pathogenesis, but also in the symptomatology of the disease.

Abscesses can and do subside without recourse to aspiration—a factor which may perhaps explain a diffidence on the part of clinicians in diagnosing abscess when pus is not demonstrated.

Some complications of abscess have been detailed. The danger of rupture of left-lobe abscesses into the pericardium is stressed.

Addendum

It is of interest to note that, since this paper has been written, Kean (1957) has stated: 'It seems clear that the only proved amebic lesion of the liver is the abscess. . . . Although subsequent studies may establish diffuse amebic hepatitis as a firm medical entity, it cannot be accepted at present.'

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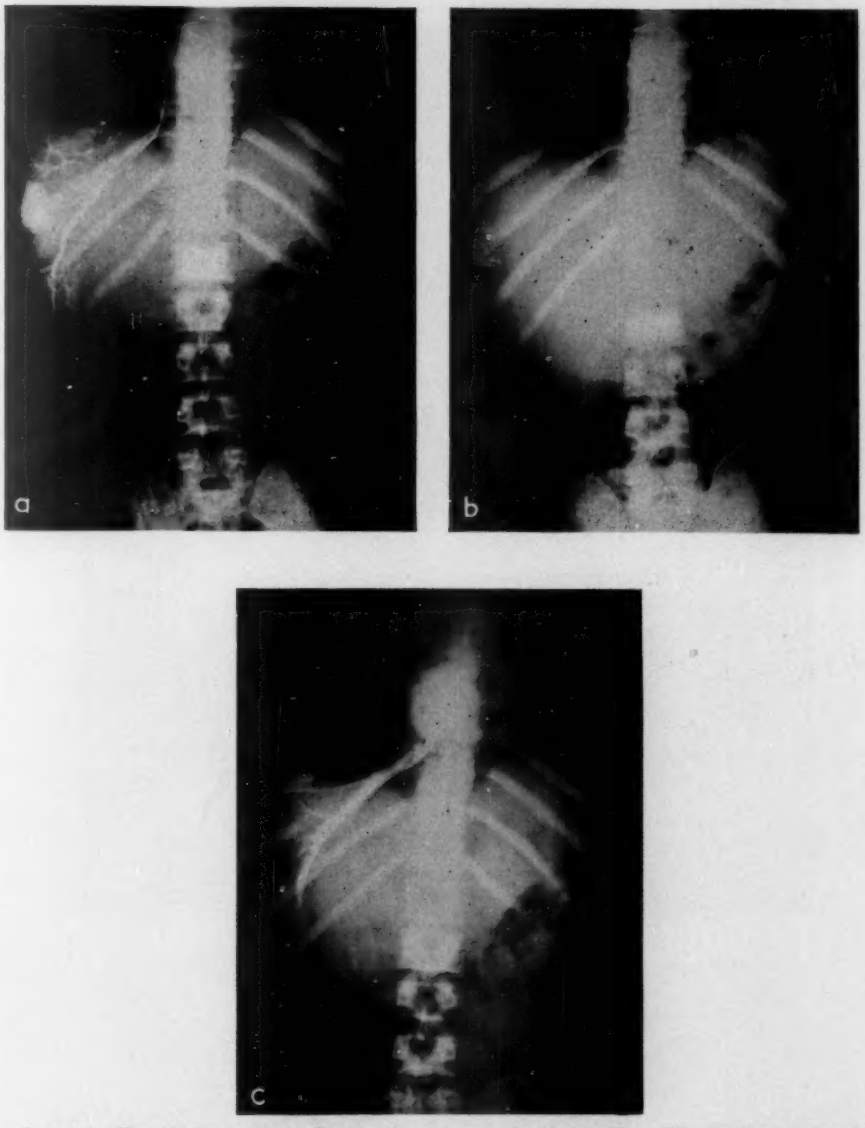

FIG. 4. (*a*) Hepatogram in a case of proven liver abscess, showing capillary filling in the abscess wall and undue patency of anastomotic venous tributaries. (*b*) Five minutes after (*a*). Dye still present in capillaries of the abscess wall. (*c*) Subsequent injection, filling the main hepatic vein tributaries without showing arborizations

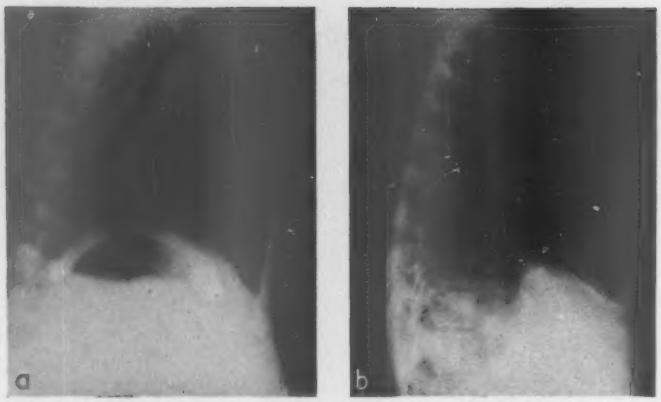

FIG. 5. (*a*) Lateral radiograph showing a large subdiaphragmatic abscess after aspiration and instillation of air. (*b*) Five weeks later, after the abscess had ruptured into the thoracic cage. Pus tracking up the greater fissure. Death followed a biliary-bronchial fistula

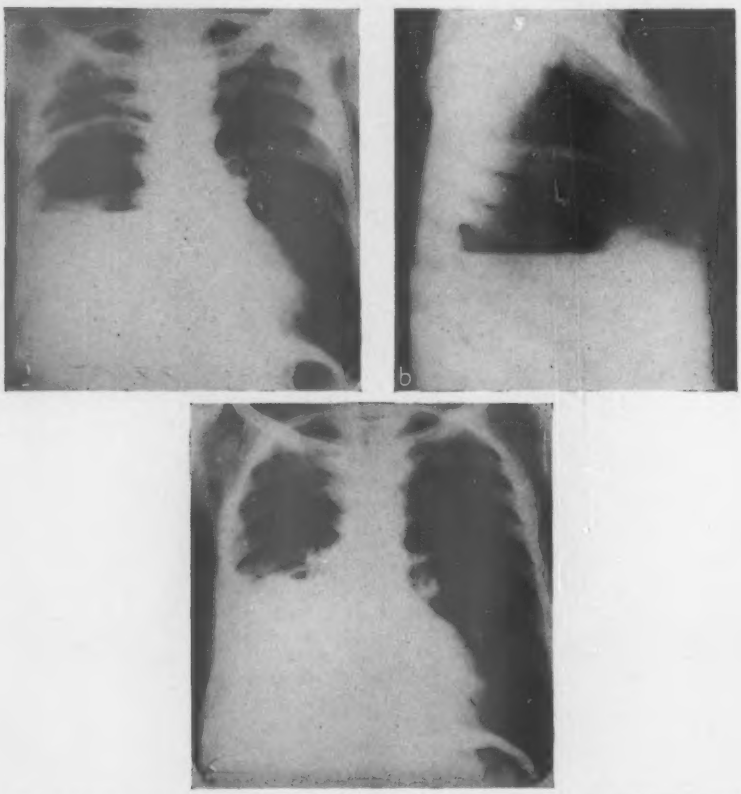

FIG. 6. (*a*) Postero-anterior radiograph of a patient with spontaneous broncho-hepatic fistula. (*b*) Lateral radiograph of the same patient. (*c*) Seven weeks later, after specific therapy. At no stage was pus aspirated

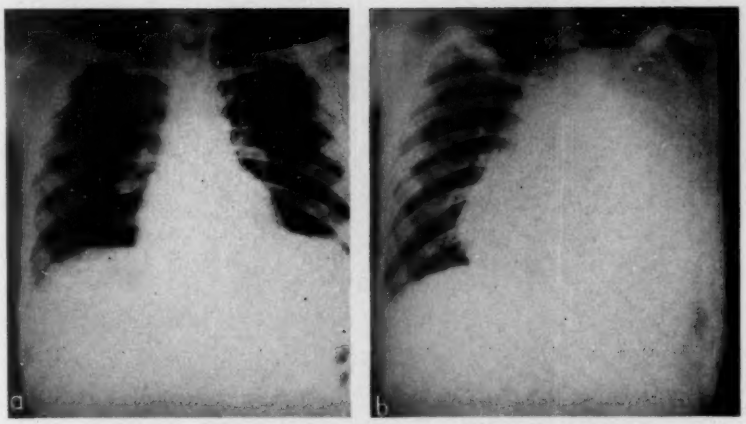

FIG. 7. (*a*) Postero-anterior radiograph showing elevation of the left diaphragm with pleural reaction at the left base. (*b*) 11 days after (*a*), showing rupture (via the anterior mediastinum) into the left pleural cavity. Two pints of pus were aspirated, and air instilled. Note the air-fluid level near the apex

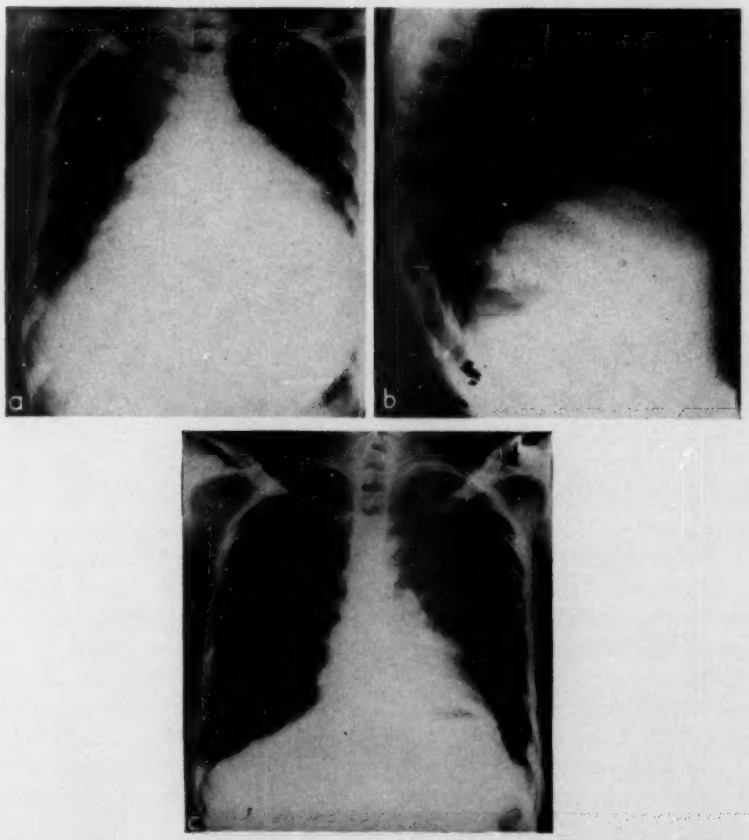

FIG. 8. Case 2. (*a*) Postero-anterior radiograph showing 'sympathetic' pericardial effusion. (*b*) Lateral radiograph eight days later, after 1,500 ml. of pus had been aspirated from the liver abscess cavity and air instilled. The level of the diaphragm is shown by the air-fluid level. (*c*) Postero-anterior radiograph of the same patient 18 days after (*a*), showing marked reduction in size of the cardiac shadow. An air-fluid level is still present in the liver

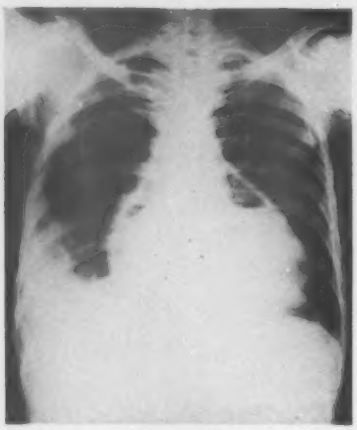

FIG. 9. Case 4. Postero-anterior radiograph after five pints of pus had been aspirated from the pericardial sac and air introduced. Note the thickened parietal pericardium

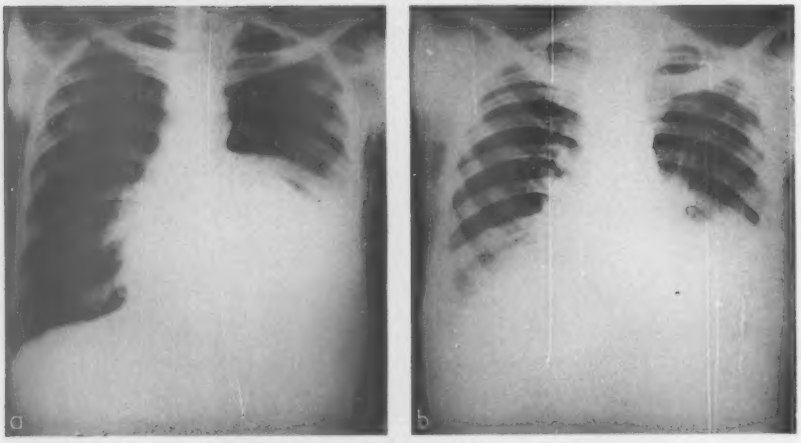

FIG. 10. Case 5. (*a*) Postero-anterior radiograph showing massive pericardial effusion. Note the air instilled after aspiration. (*b*) Postero-anterior radiograph one month later, after surgical drainage. A left pleural empyema has developed

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CARCINOMA OF THE OESOPHAGUS WITH KERATOSIS PALMARIS ET PLANTARIS (TYLOSIS)[1]

A Study of Two Families

By W. HOWEL-EVANS, R. B. McCONNELL, C. A. CLARKE and P. M. SHEPPARD

(From the Department of Medicine, University of Liverpool)

With Plates 45 and 46

Keratosis palmaris et plantaris (tylosis) is usually considered to be an inherited disability of a comparatively trivial kind. That it sometimes may have a sinister significance is shown by this study of two Liverpool families with tylosis, in which 18 members have developed carcinoma of the oesophagus. A preliminary letter on the subject has already appeared in the *British Medical Journal* (Clarke, Howel-Evans, and McConnell, 1957).

Tylosis

1. *General features.* Tylosis is one of many forms of dyskeratosis which have been well classified by Cockayne (1933). Its most conspicuous feature is great thickening of the skin of the palms and soles, and hyperhidrosis is also commonly present. Rarely the condition is confined to the soles. Microscopically there is general hypertrophy of all the layers of the skin, the epidermis being chiefly affected; in addition there is hypertrophy of the sweat glands and their ducts (Cockayne, 1933). In many patients with the abnormality the horny epidermis is shed at intervals in large flakes, or as a complete cast of the palm or sole, and this takes place as a rule every autumn; it leaves a red, tender surface, which soon becomes overgrown again with thick epidermis (Cockayne, 1933).

2. *Associated abnormalities* are rare. Cockayne (1933) quoted Hanhart, who described a Swiss family, the affected members of which developed tylosis at the age of 15 years and multiple lipomata at the age of 22. Cockayne commented that the late age at which the tylosis appeared made it doubtful whether it was the ordinary form of the disease. Many other abnormalities have been described in association with tylosis in isolated patients, but genetic linkage was not demonstrated in any of these cases. We have found no reports in the literature of an association between tylosis and malignant disease of other parts of the body, although Sequeira, Ingram, and Brain (1947) mentioned a case in which epitheliomatous change occurred in the skin of a tylotic patient's hand.

[1] Received December 6, 1957.

3. *The incidence* of the condition has recently been calculated in Northern Ireland by Swan (1956) as one in 40,000; no other figures are available.

4. *Inheritance.* Tylosis appears to be controlled by a single autosomal gene with high penetrance and heterozygous effect. 'Men and women are equally affected and no race is immune' (Scott, 1953). There are at least two types of inherited tylosis. Lawler and Renwick (1957) are of the opinion that the two main forms run true in families and are, therefore, due to different genes. They consider that these forms can be easily distinguished from each other as follows: type A (found in the two families described below), which has a rather variable age of onset from five to 15 years; and type B, diagnosable in the first year of life, and distinguishable clinically from type A by the sharply delimited edges of the lesion, by the uniform thickness of the keratosis, and by the relative rarity of painful fissuring. Lawler and Renwick have found no evidence of an association of type B with carcinoma of the oesophagus in three large families studied. Both genetic types are dominant. In the 47 families collected by Cockayne (1933) the proportion of affected to normal members was 594 to 483. Such an excess of affected persons above expectation is liable to arise in the collection of this type of data, owing primarily to the small size of human families; it should not be taken to mean that a proportion of the parents were homozygous tylotics, and, therefore that the homozygous expression of the gene has ever been examined. In fact, Cockayne's families accord well with the hypothesis that the great majority of the matings were between heterozygous and normal subjects. The sex ratio in the tylotics approaches unity, 318 male to 284 female subjects in Cockayne's families.

The Affected Families

The two families will now be described. It is probable that they are in fact related (see page 456) but, as the fact has not been firmly established, each family will be described separately.

Family S

The present study was initiated by the admission to Broadgreen Hospital, Liverpool, in 1956, of the propositus (S III, 53), a man aged 37 with tylosis. He complained of three months' progressive difficulty in swallowing, and was found to have a carcinoma of the oesophagus, which subsequently was removed. He stated that his father also had had tylosis and that he had died at the age of 63 in the same hospital, in 1953, of carcinoma of the oesophagus. This was confirmed from the records. During the time that the propositus was in hospital it was discovered that one of his cousins (S IV, 51) was in another Liverpool hospital because of dysphagia. He also had tylosis, and at operation a carcinoma of the oesophagus was removed. In view of these three cases we decided to study the incidence of tylosis and of carcinoma of the oesophagus in family S, and the pedigree of this family is shown in Fig. 1. Table I A gives

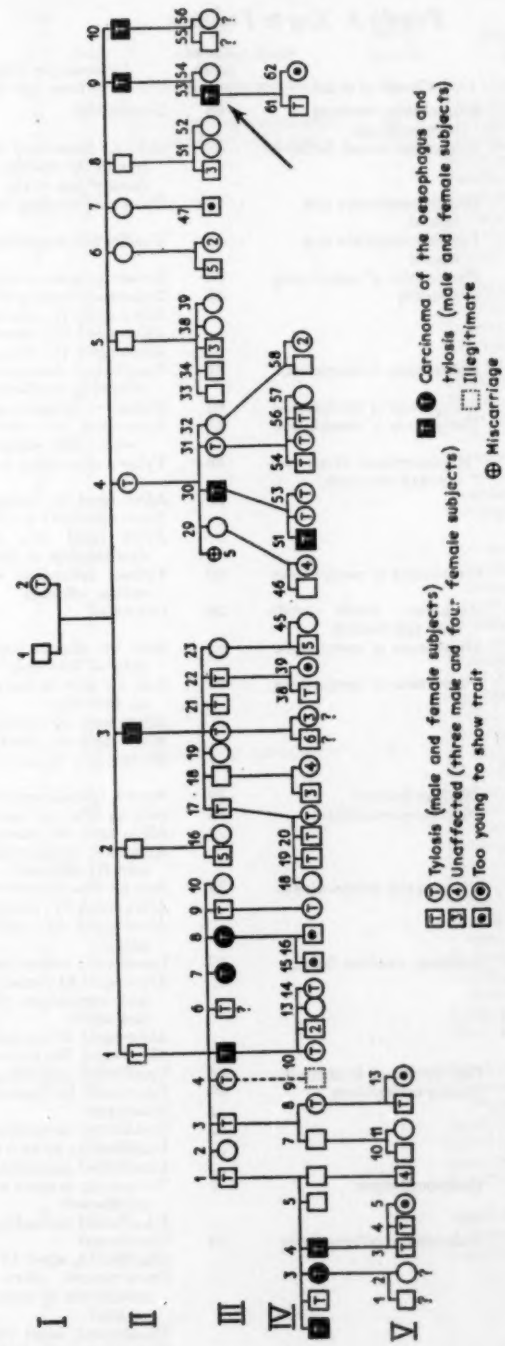

FIG. 1. Family S.

Family S: Key to Pedigree

Generation	*Member*	*Tylosis (T)*	*Sex*	*Cause of death*	*Age at death (years)*	*Grounds for diagnosis of tylosis; age if alive*
I	1	..	m	Bronchitis, cerebral haemorrhage	63	Unaffected
	2	T	f	Dementia, renal cirrhosis	63	Said to have had hard skin on hands by several members of family (see text)
II	1	T	m	Death certificate not traced	c. 70	Tylosis according to family
	2	..	m	Death certificate not traced	c. 45	Unaffected according to family
	3	T	m	*Carcinoma of oesophagus*	48	Severe tylosis according to family
	4	T	f	Dementia	65	Tylosis according to family
	5	..	m	..	..	Alive aged 75; examined
	6	..	f	..	..	Alive aged 72; examined
	7	..	f	..	..	Alive aged 71; examined
	8	..	m	Pulmonary tuberculosis	53	Unaffected according to wife; offspring unaffected
	9	T	m	*Carcinoma of oesophagus*	63	Father of propositus (see text)
	10	T	m	*Carcinoma of oesophagus*	45	According to sibs his hands 'peeled like onions'
III	1	T	m	'Haemorrhage from carcinoma stomach'	48	Tylosis according to sibs
	2	..	f	..	..	Alive aged 70; examined
	3	T	m	..	..	Alive aged 65; tylosis seen
	4	T	f	..	..	Alive aged 58; tylosis, predominantly on feet, seen
	5	T	m	*Carcinoma of oesophagus*	46	Tylosis according to wife; offspring affected
	6	? T	m	Accident; death certificate not traced	26	Doubtful
	7	T	f	*Carcinoma of oesophagus*	52	Said by sibs to have had hard skin on feet only
	8	T	f	*Carcinoma of oesophagus*	46	Said by sibs to have had tylosis on feet only
	9	T	m	..	..	Alive aged 53; tylosis seen
	10	..	f	..	..	Alive aged 46; examined
	11–16	..	5 m, 1 f	..	..	No tylosis; 14 and 15 seen
	17	T	m	Cardiac failure	59	Severe tylosis according to wife
	18	..	m	Bronchopneumonia	56	Said by sibs not have had tylosis
	19	..	f	..	..	Alive aged 60; examined
	20	T	f	..	..	Affected; examined. Offspring also (?) affected
	21	T	m	Pulmonary tuberculosis	29	Said by sibs to have been affected
	22	T	m	..	..	Alive aged 47; examined
	23	..	f	..	..	Alive aged 42; unaffected; examined
	29	..	f	Asthma, cardiac failure	40	Unaffected according to sibs
	30	T	m	..	..	Alive aged 64; examined; tylosis and *carcinoma of oesophagus* (see text)
	31	T	f	..	..	Alive aged 57; examined
	32	..	f	..	..	Alive aged 54; examined
	33	..	m	Carcinoma of bronchus	42	Unaffected according to sibs
	34	..	m	Status epilepticus	30	Examined (a 'spastic')
	35–7	..	m	..	..	Examined
	38–39	..	f	..	..	Unaffected according to sibs
	40–44	..	m	..	..	Unaffected; 41 and 43 examined
	45–46	..	f	..	..	Unaffected according to sibs
	47	..	m	Gastroenteritis	1	Too young to show trait; mother unaffected
	48–50	..	m	..	..	Unaffected according to sibs
	51	..	f	Pulmonary tuberculosis	20	Unaffected
	52	..	f	..	..	Unaffected, aged 47; examined
	53	T	m	..	..	PROPOSITUS, alive aged 38; *carcinoma of oesophagus*; examined
	54	..	f	..	..	Unaffected, aged 33; examined
	55–6	?	m, f	..	..	Not yet traced; father tylotic

Generation	*Member*	*Tylosis (T)*	*Sex*	*Cause of death*	*Age at death (years)*	*Grounds for diagnosis of tylosis; age if alive*
IV	1	T	m	*Carcinoma of oesophagus*	43	Said by sibs to have had tylosis
	2	T	m	..	..	Examined
	3	T	f	*Carcinoma of oesophagus*	37	Feet affected according to sibs
	4	T	m	*Carcinoma of oesophagus*	44	Tylosis, examined
	5	..	m	..	..	Unaffected, aged 42; examined
	6	..	m	..	..	Unaffected, aged 41; examined
	7	..	m	..	..	Unaffected, aged 44; examined
	8	T	f	..	..	Tylosis, examined; aged 38
	9	..	m	..	..	Unaffected, aged 35; examined
	10	T	f	..	..	Tylosis of feet; examined; aged 29
	11–12	..	m	..	..	Unaffected according to sibs
	13	..	f	..	..	Unaffected, aged 21; examined
	14	T	f	..	..	Tylosis, examined; aged 18
	15	..	m	..	..	Examined, aged 12; too young to show trait
	16	..	m	..	..	Aged 7; too young to show trait
	17	T	f	..	..	Examined; aged 22
	18	..	f	..	..	Aged 23, unaffected according to sibs
	19	T	m	..	..	Examined, aged 22
	20	T	m	..	..	Examined, aged 17
	21	T	f	..	..	Examined, aged 12
	22–28	..	3 m, 4 f	..	..	Not traced; said to be unaffected
	29–37	..	6 m, 3 f	..	..	Not co-operative; according to mother tylosis known in two males
	38	T	m	..	..	Examined, aged 17
	39	..	f	..	..	Examined, aged 13; too young to show trait
	40–44	..	m	..	..	Examined, aged 6 to 22
	45	..	f	..	..	Aged 3
	46	..	m	..	..	Aged 30; unaffected according to sibs
	47–50	..	f	..	..	Examined, aged 20 to 25
	51	T	m	*Carcinoma of oesophagus*	34	Examined
	52	T	f	..	..	Examined, aged 22
	53	T	f	..	..	Examined, aged 25
	54	T	m	..	..	Examined, aged 25
	55	T	f	..	..	Examined, aged 19
	56	T	m	..	..	Examined, aged 15
	57	..	f	..	..	Examined, aged 14
	58	..	m	..	..	Unaffected according to mother; aged 23
	59–60	..	f	..	..	Unaffected according to mother; aged 25–27
	61	T	m	..	..	Examined, aged 9
	62	?	f	..	..	Examined, aged 6; too young to show trait
V	1	?	m	..	..	Aged 17 } would not allow ex-
	2	s	f	..	..	Aged 13 } amination, but said by father to be unaffected
	3	T	m	..	..	Aged 16
	4	T	m	..	..	Examined, aged 11; clear evidence of tylosis
	5	..	f	..	..	Aged 10; too young to show trait
	6–9	..	m	..	..	Aged 2 to 8
	10	..	m	..	..	Aged 16 } said by father (regis-
	11	..	f	..	..	Aged 12 } tered nurse) to have normal skin
	12	T	m	..	..	Aged 10, examined; clear evidence of tylosis
	13	..	f	..	..	Aged 13; too young to show trait

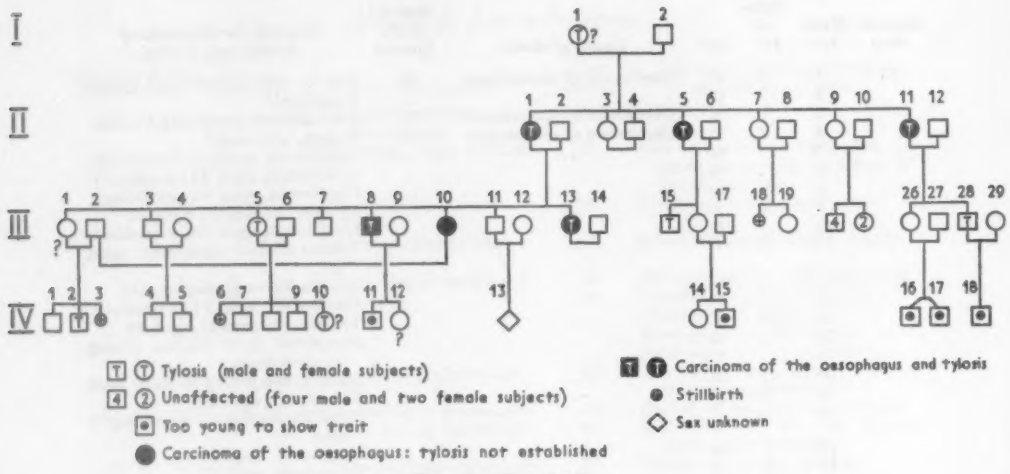

FIG. 2. Family C.

Family C: Key to Pedigree

Generation	*Member*	*Tylosis (T)*	*Sex*	*Cause of death*	*Age at death (years)*	*Grounds for diagnosis of tylosis; age if alive*
I	1	? T	f	Rheumatic endocarditis	70	Hands said to have been normal, but had trouble with feet. Said to have been adopted
	2	..	m	Cardiac disease and renal coma	63	No tylosis in collaterals
II	1	T	f	*Carcinoma of oesophagus*	53	Offspring tylotic
	3	..	f	Rheumatoid arthritis	*c.* 50	Hands said to have been normal
	5	T	f	*Carcinoma of oesophagus*	49	Hands said by daughter to have been affected; son tylotic
	7	..	f	Toxaemia of pregnancy	24	No information about skin elicited
	9	..	f	..	..	Alive; would not allow interview; 6 offspring non-tylotic
	11	T	f	*Carcinoma of oesophagus*	57	Tylosis described by husband; son tylotic
III	1	? T	f	Childbirth	*c.* 35	Said by husband not to have been tylotic, but son affected (see text)
	3	..	m	..	..	Alive aged 54; examined
	5	T	f	..	..	Alive aged 52; examined
	7	..	m	Cerebral haemorrhage	25	Not known to have been tylotic
	8	T	m	*Carcinoma of oesophagus*	37	Widow states hands and feet were affected
	10	..	f	*Carcinoma of oesophagus*	32	Tylosis not established (see text)
	11	..	m	..	..	Alive aged 37; not known to have been tylotic
	13	T	f	*Carcinoma of oesophagus*	29	Husband states tylosis of feet only
	14	..	m	..	..	Alive aged 40; examined
	15	T	m	..	..	Alive and well aged 43; states he has tylosis
	16	..	f	..	..	Alive aged 42; examined
	17	..	m	..	..	Alive
	19	..	f	?	Childhood	..
	20–25	..	4 m, 2 f	..	..	Alive and well; said not to have tylosis
	26	..	f	..	..	Aged 36; said not to have tylosis
	28	T	m	..	..	Alive aged 32; examined

Generation	*Member*	*Tylosis (T)*	*Sex*	*Cause of death*	*Age at death (years)*	*Grounds for diagnosis of tylosis; age if alive*
IV	1	..	m	..	..	Alive aged 29; examined
	2	T	m	..	..	Alive aged 24; examined
	4–5	..	2 m	..	..	Alive; examined
	7	..	m	Meningitis	?	..
	8–9	..	m	..	..	Alive aged 24 and 25; mother would not allow interview
	10	? T	f	..	..	Alive aged 18; examination refused, but handshake suggested tylosis
	11	..	m	?	Childhood	..
	12	..	f	..	..	Aged 16; not traced
	14	..	f	..	..	Aged 19; examined
	15	..	m	..	..	Aged 8; examined
	16–17	..	m	..	..	Aged 8; identical twins
	18	..	m	..	..	Aged 4; examined

the numbers of those affected and unaffected by tylosis in different generations of family S. The first member (S I, 1) came to Liverpool from Bristol in 1860 as a ropery apprentice, and tradition in the family attributes the tylosis to this occupation, which causes palmar callosities. In fact, the condition was almost certainly brought into the family by his wife (S I, 2) who was born in Liverpool in 1845. An elderly relative, who remembers her well, commented that 'she would never shake hands with people unless she was wearing gloves, as she was very sensitive about her hands'. It is also of interest that at a post-mortem examination in 1907 it was noted that there was thickening of the oesophagus. Since tylosis is so striking, statements such as these have usually been taken throughout the survey to be diagnostic of the condition. Furthermore, such observations of relatives have often been confirmed by cases occurring in descendants.

Comments on family S. 1. *Type of tylosis.* The tylosis seen in family S, although late in onset (usually about 14 years) is of the diffuse type and associated with hyperhidrosis (Plate 45, Figs. 3 and 4). Representative patients were referred to Dr. Douglas G. Freshwater, and he confirmed the view that the condition was the form of tylosis commonly met with in dermatological practice. The keratoses were easily recognizable as smooth, yellowish thickenings of the skin of the palms and soles. The lesions were often gross in manual workers, and invariably less severe in women. They were said to be a nuisance by many of the affected men, and it was often necessary, when the thickenings were marked, for them regularly to shave their plantar keratoses with razors. Few, however, had ever sought medical advice about the condition, though four had been discharged from the Services because they were unable to wear boots. Striking temporary regression of the tylosis was seen in two patients (S III, 53 and IV, 51) while convalescent after oesophagogastrectomy for carcinoma of the oesophagus, though it recurred subsequently. This regression has also been noted in women after parturition or illnesses. Two adult women (S III, 4 and IV, 53), both the offspring of tylotic fathers, were seen to have gross hyperkeratosis of the soles of the feet only, the palms being normal; the inheritance of tylosis by their descendants could not be demonstrated, one woman having an illegitimate son whose skin is normal, and the two children of the other

being too young to show the trait. Three other women (S III, 7 and 8, and IV, 3), who had died of carcinoma of the oesophagus, were said by their siblings to have had thick skin on their feet only. It was not possible to demonstrate the inheritance of tylosis in the children of these patients, as S IV, 15 and 16 are too young to show the trait, S V, 1 and 2 would not be interviewed, and S III, 7 was unmarried. But in view of the findings in S III, 4 and IV, 53 it seems

TABLE I

Numbers Affected and Unaffected with Tylosis in the Two Families

A. *The S Family*

Generation	*Male members*				*Female members*				*Total*			
	A	*U*	*?*	*Total*	*A*	*U*	*?*	*Total*	*A*	*U*	*?*	*Total*
I . .	..	1	..	1	1	..	..	1	1	1	..	2
II . .	4	3	..	7	1	2	..	3	5	5	..	10
III . .	9	19	3	31	5	14	1	20	14	34	3	51
IV . .	10	16	8	34	9	14	5	28	19	30	13	62
Total . .	23	39	11	73	16	30	6	52	39	70	16	125
In Tylotic sibships												
II . .	4	3	..	7	1	2	..	3	5	5	..	10
III . .	9	1	1	11	5	7	..	12	14	8	1	23
IV . .	10	5	..	15	9	3	2	14	19	8	2	29
Total . .	23	9	1	33	15	12	2	29	38	21	3	62

B. *The C Family*

Generation	*Male members*				*Female members*				*Total*			
	A	*U*	*?*	*Total*	*A*	*U*	*?*	*Total*	*A*	*U*	*?*	*Total*
I . .	..	1	..	1	1	..	..	1	1	1	..	2
II . .	..	..	..	..	3	3	..	6	3	3	..	6
III . .	3	7	..	10	2	6	1	9	5	13	1	19
IV . .	Insufficient data											
Total . .	3	8	..	11	6	9	1	16	9	17	1	27

Those too young to show trait are included in the columns headed ?

almost certain that S III, 7 and 8 and S IV, 3 were also tylotic subjects. Tylosis confined to the hands was not observed in any member of the family.

2. *Carcinoma of the oesophagus.* It will be seen from the pedigree that all the 12 patients with carcinoma also had tylosis. In six cases sections of the oesophagus were examined histologically by Dr. F. Whitwell. He reported that the growths were all of the squamous-cell type, well differentiated and showing no unusual characteristics. In four patients (S III, 5 and 7; IV, 3 and 4) clinical and radiological grounds provided the evidence for the diagnosis. In one case (S II, 3) there are no details other than the death certificate, which states that the man died in 1917 of carcinoma of the oesophagus. The remaining patient (S III, 30) is of considerable interest. He is a tylotic subject aged 64, who, though without oesophageal symptoms, had an oesophagoscopy carried out at our request while he was being investigated for a suspected carcinoma of the bronchus. Thickening of the mucosa at the lower end of the oesophagus was seen, and a small specimen taken from this area revealed a carcinoma of the

TABLE II

Details of Patients with Carcinoma of Oesophagus

Patient	*Tylosis (T)*	*Sex*	*Age at onset of carcinoma*	*Year of death*	*Site of carcinoma*	*Grounds for diagnosis of carcinoma of oesophagus*
S Family						
II, 3	T	m	46	1917	?	Death certificate only; no clinical data available. Said to have had post-mortem examination; no record found
II, 9	T	m	61	1953	Lower third	Full clinical records, operative and post-mortem findings; had leucoplakia of oesophagus. Squamous-cell carcinoma
II, 10	T	m	44	1936	Lower third	Full clinical data and post-mortem findings. Squamous-cell carcinoma
III, 5	T	m	46	1946	Lower third	Clinical data with radiological findings only
III, 7	T	f	52	1956	Lower third	Clinical data and radiological findings only
III, 8	T	f	43	1951	Lower third	Clinical data and radiological findings only
III, 30	T	m	64	..	Lower third	Found to have squamous-cell carcinoma on biopsy, May 1957, when asymptomatic; dysphagia developed in October 1957 (see text)
III, 53	T	m	37	..	Lower third	PROPOSITUS. Full clinical and operative data. Squamous-cell carcinoma
IV, 1	T	m	43	1951	Middle third	Full clinical and operative data. Squamous-cell carcinoma
IV, 3	T	f	37	1949	Lower third	Clinical and radiological data; biopsy from oesophageal stricture: squamous-cell carcinoma
IV, 4	T	m	44	1957	Lower third	Clinical; radiological confirmation; permission for autopsy refused
IV, 51	T	m	34	1957	Middle third	Full clinical, radiological, and operative findings; died of post-operative recurrence of tumour. Squamous-cell carcinoma
C Family						
II, 1	T	f	53	1935	?	Death certificate only (hospital notes not available)
II, 5	T	f	49	1934	?	Death certificate; gastrostomy performed; no clinical data found
II, 11	T	f	57	1951	Lower third	Full clinical, radiological, and operative findings; autopsy. Poorly differentiated squamous-cell carcinoma
III, 8	T	m	37	1947	Lower third	Full clinical and X-ray data; oesophagoscopy showed a stricture 34 cm. from the teeth. No biopsy
III, 10	Not established	f	32	1945	Upper third	Clinical and radiological data. Oesophagoscopy: biopsy showed poorly differentiated squamous-cell carcinoma
III, 13	T	f	29	1951	Lower third	Clinical, radiological, and post-mortem findings

Total number of cases: 18 (S family 12, C family 6). Male patients, 10. Female patients, 8.
Average age at onset: 44·7 (S family 45·7, C family 42·8) years.
Sites: lower third, 12; middle third, 2; upper third, 1; not known, 3.

oesophagus (Plate 46, Figs. 5 and 6). Dr. Whitwell has reported on the biopsy specimen as follows: 'The section shows a layer of hyperplastic squamous epithelium and an infiltration by lymphoid cells in the subepithelial tissues. In addition there is an area where the epithelium has changed in character and is invading the subepithelial tissues. This invasion takes the form of ring-like downgrowths of very well differentiated squamous carcinoma.' The radiological findings which at first suggested carcinoma of the bronchus have now disappeared. The patient, having no symptoms referable to an oesophageal lesion, was very loath to undergo surgical treatment, which had been unsuccessful in his son (S IV, 51). He was kept under observation; five months later dysphagia developed, and an extensive tumour of the lower third of the oesophagus was removed. Of the 12 patients with carcinoma of the oesophagus, only two in this family are alive. The sites of the oesophageal lesion were as follows: lower third, nine cases; middle third, two cases; site unknown, one case.

3. *Analysis of deaths.* (1) *Subjects with tylosis.* Seventeen persons known to have been tylotic have died; the causes of death were:

Carcinoma of the oesophagus	10
Carcinoma of the stomach (S III, 1)	1
Dementia (S I, 2 and II, 3)	2
Heart failure (S III, 17)	1
Accident (S III, 6)	1
Pulmonary tuberculosis (S III, 21)	1
Not known	1

It seems possible that the man certified as having died from haemorrhage from carcinoma of the stomach (S III, 1) had, in fact, an oesophageal neoplasm. Three of his offspring developed oesophageal carcinoma, one son dying of haemorrhage from perforation of the aorta by the growth. In one of the subjects who died of dementia (S, I, 2), the woman referred to on page 419, it was noted *post mortem* in 1907 that there was thickening of the oesophagus, but it was not examined histologically.

(2) *Subjects without tylosis.* Of the 71 persons unaffected by tylosis, 10 are known to have died. In only one of these was there malignant disease, a man aged 43 (S III, 33) who developed carcinoma of the bronchus. The causes of death in the remaining nine were as follows:

Bronchitis and cerebral haemorrhage (S I, 1)	1
Pulmonary tuberculosis (S II, 8 and III, 52)	2
Bronchopneumonia (S III, 18)	1
Asthma, heart failure (S III, 29)	1
Status epilepticus (S III, 34)	1
Gastroenteritis (S III, 47)	1
'Accidents' (not confirmed by death certificates) (S II, 2 and III, 11)	2

Family C

This family was reported by Clarke and McConnell (1954) because six cases of carcinoma of the oesophagus had occurred in two generations. Reasons were

given for thinking that the cancer might have been due to a single gene with heterozygous effects. At that time the fact that the family was tylotic had not been appreciated, because the members with carcinoma had not been seen, when alive, by the authors. After the discovery of family S, family C was re-investigated from the point of view of tylosis, and it was found that this family also had the skin condition. Five of the six patients who had died of the carcinoma were tylotic; as they were dead before the investigation began, it was necessary to rely on relatives' descriptions of their hands and feet, and on the finding of tylosis in the descendants (C III, 5 and 28) of two of them. In the sixth patient (C III, 10)* the presence of tylosis cannot be established or excluded, and she is therefore not scored as affected, though the following facts are pertinent. The husband of this woman (C III, 2) had previously been married to one of her sisters (C III, 1). There are two sons of this first marriage, one of whom has well-marked tylosis (C IV, 2). The husband states that both wives had entirely normal skin, but this statement is likely to be incorrect, at least with regard to the first wife, one of whose offspring is tylotic; it would seem either that he was unobservant or that the lesions were confined to the feet, as is known to have been the case in two of his wives' sisters (C III, 5 and III, 13).

Comments on family C. 1. *Type of tylosis.* This was similar to that found in family S, the condition not appearing until after childhood. The numbers affected and unaffected with tylosis are shown in Table I B, and Fig. 2.

2. *Carcinoma of the oesophagus.* In the three cases in which the histology is known (C II, 11; III, 10 and 13) the growth was a squamous-cell carcinoma (Dr. F. Whitwell). The grounds for the diagnosis in two patients, who died in 1934 and 1935 (C II, 1 and 5), are not known, but death was certified as being due to carcinoma of the oesophagus. In the sixth case (C III, 8) the carcinoma was seen at oesophagoscopy, but no biopsy report is available. The site of the cancer is known with certainty to have been the lower end of the oesophagus in three of the six cases (C II, 11; III, 8 and 13). In another (C III, 10) the growth was in the upper third. In one (C II, 5) the symptoms suggest that it was in the middle or lower third, and in another (C II, 1) the site is not known.

3. *Analysis of deaths.* (1) *Subjects with tylosis.* Seven persons known to have been affected with tylosis have died; the causes of death were:

Carcinoma of the oesophagus	5
Childbirth (C III, 1)	1
Rheumatic endocarditis (C I, 1) (tylosis not diagnosed with certainty)	1

(2) *Subjects without tylosis.* Of those not known to have had tylosis, four have died; the causes of death were:

Carcinoma of the oesophagus (C III, 10) . .	1 (see above*)
Rheumatoid arthritis (C II, 3)	1
Toxaemia of pregnancy (C II, 7)	1
Cerebral haemorrhage (C III, 7)	1

Further Observations on the Two Families

It is considered likely that the two families S and C are related; both families have the same unusual association of disease, come from the same part of Liverpool, and are of the same social status. An extensive search has been made to establish a connexion between them, but, despite much information from family records and parish-registers, it has not been possible to establish a definite relationship. As the first woman of family C (C I, 1) is thought by several members of the family to have been adopted, she may have been the link. It is probable, to judge from relatives' statements, that she had tylosis, especially as no tylosis is known in her husband's family, of which the descendants of other members were visited.

Collection of data. In an investigation such as this the help of relatives is essential. Most of them were visited personally by one of us (W. H.-E.) and in general they were very co-operative. Tylosis was made the subject of inquiry, and cancer was not mentioned. Details of occupation, social status, and tobacco and alcohol consumption were noted, and a general inquiry made as to past illnesses. The clinical examination was limited to a scrutiny of the hands and feet, to find out whether or not tylosis was present. Where members of the family had died, the causes of death were established from the Registrars of Births and Deaths, and other details were often available from family doctors and hospital records. Fortunately, in neither family had the majority of members realized the high incidence of cancer among their relatives; but in family S there were two exceptions to this, and both persons concerned were asked to attend for barium-swallow radiography, which gave normal results. It was possible to obtain a similar investigation (also with a normal result) in the patient C III, 5 while she was in hospital for treatment of a psychoneurosis. Examination by oesophagoscopy of healthy tylotic subjects was not considered justifiable, as the procedure is not entirely free from risk, and we were anxious to avoid fostering carcinophobia.

Social status. Classification was carried out according to the Registrar-General's grading, and our assessment was made when the relatives were visited in their homes. The social status of family C was commented on in an earlier paper, and the possibility was mentioned that a concentration of the carcinoma in one branch of the family in the second generation might have been connected with their decline in economic status (Clarke and McConnell, 1954). In family S about one-third of the members belonged to Class III (skilled artisans), and a few to Class V (unskilled artisans), but the majority were in Class IV. This family, in contrast to family C, shows no correlation between economic status and the incidence of carcinoma of the oesophagus.

Dietetic factors. Irregularities of food and drink are commonly considered to be of importance in carcinoma of the oesophagus, and abuse of alcohol has been incriminated. Thus Clemmesen (1951) showed that the incidence of the disease is higher in commercial travellers, barmen, and waiters than among those engaged in other trades. These occupations do not figure in either of our

two families. An inquiry into the diet of the propositus (S III, 53) and that of his cousin (S IV, 51), after their operations for the removal of oesophageal carcinoma, showed that both patients had had an adequate diet before the onset of their illness, but that they had very different habits. Thus the propositus, while virtually teetotal, ate his food very hot, whereas the cousin, who had an alcohol and tobacco consumption above the average, preferred his meals cold. It has been suggested (Porter, 1951) that patients with tylosis tend to have low serum levels of vitamin A and carotenoids. Dencer (1953), on the other hand, was sceptical of this relationship, and quoted H. M. Sinclair, who thought that the metabolism of essential fatty acids was more likely to be implicated. We are investigating this possibility in our two families.

The oesophageal lesion. The possibility was considered that the gene responsible for tylosis in these families might also cause a precancerous lesion in the oesophagus. Leucoplakia of the oesophagus, without carcinoma, is not uncommon in routine post-mortem material, but both Willis (1953) and Evans (1956) considered that its role in the development of oesophageal cancer had not been established. In the S and C families only one case of leucoplakia (S II, 9) was found; and in the patient described on page 420 (S III, 30), with an initially asymptomatic oesophageal carcinoma, leucoplakia was absent. Leucoplakia was not commented on in the four oesophagoscopy reports which are available. Furthermore, in six cases the thickness of the squamous epithelium adjacent to the carcinoma was measured, and was from 30 to 80μ. These figures did not differ from those obtained in a control group consisting of 12 comparable sections from other patients with carcinoma of the oesophagus. In this connexion the work of Steiner (1956) is of interest. In nine presymptomatic carcinomas of the oesophagus, which he found among 9,000 consecutive autopsies, none appeared to have originated in a perceptible pre-existing lesion of the epithelium, which was thinned and atrophic more often than thickened. The evidence, therefore, suggests that the tylosis gene in the two families does not cause a keratotic lesion in the oesophagus.

Genetics. Any genetic interpretation of the association between tylosis and carcinoma of the oesophagus in these two families must take into account the following facts: (1) The association has never been reported previously, and therefore is probably very rare. Since we became acquainted with it we have investigated three other tylotic families, two showing an early and one a late onset. In none of them did we discover a case of carcinoma of the oesophagus; nor did Lawler and Renwick in the three large families referred to on page 414. (2) There has been no previous convincing evidence that carcinoma of the oesophagus ever has any hereditary basis. Mosbech and Videbaek (1955), in a large survey of the disease in Denmark, emphasized the fact that the disease was no more common among relatives of those affected than in the general population.

It is obvious, however, that in our families there is a marked association between tylosis and carcinoma of the oesophagus, since out of 48 tylotic members 18 have developed the neoplasm, whereas among 87 non-tylotic members

there has been only one case of oesophageal cancer, and it is possible that this patient (C III, 10) was, in fact, tylotic (see page 423). The pedigrees give clear evidence that the tylosis is inherited (as is usually the case) as an autosomal gene with heterozygous expression. Thus about half the number of offspring of tylotics are themselves tylotic, and both male and female offspring of a male tylotic can show the trait, thereby excluding sex-linkage. A recessive method of inheritance can be rejected, because there has been no marriage between close relatives.

The association of tylosis with oesophageal carcinoma in our families could have several genetic explanations—a single mutant, a modifying gene, or a separate gene for carcinoma of the oesophagus. The most likely explanation is that a single gene, the result of a mutation, is responsible, and that it is not the gene which is the usual cause of tylosis. This mutant (whether or not it is at the same locus as the normal tylotic gene) might always cause carcinoma of the oesophagus provided the individual lived long enough, or might only cause it in certain environmental conditions. If there were a decrease in the proportionate incidence of the cancer in tylotic persons aged 80 or 90 years, it would be evidence in favour of some important environmental factor, but there are not enough old people in these pedigrees to test the point. The second genetic explanation would be that the normal gene for tylosis causes carcinoma of the oesophagus in the presence of another gene or genes (modifiers) which do not themselves cause oesophageal cancer. If such modifiers were extremely closely linked with the tylotic gene, the association would be found as it occurs in these two families, the two conditions being inherited together. It is impossible, from the data shown, to differentiate between a closely linked modifier and a single mutant. On the other hand, unlinked modifiers would have to be extremely common in the population to cause the association in so many of the tylotic members of our families, and, if they were sufficiently common, the association would be found in many other tylotic families, whereas it has not previously been described. An unlikely explanation is that there are two closely linked genes, one producing tylosis and the other cancer of the oesophagus. If this were the case it would be expected that occasionally, when crossing over occurred, families would be found in which carcinoma of the oesophagus was inherited as a single dominant without the tylosis; but such a finding has never been described.

In a condition such as tylosis, in which the disorder is a heterozygous effect and has a high degree of penetrance, it is well worth while to test for linkage between the genes controlling the disorder and those of the various blood-group systems. This has been done in some members of the two families by Dr. Sylvia D. Lawler, of the Galton Laboratory, but she has not demonstrated that any such close linkage exists.

Discussion

It is well recognized that the concentration of cancer in families may occur by chance, and Steiner (1956) was of the opinion that this was the case in

family C when it was reported in a previous paper (Clarke and McConnell, 1954). Subsequent events have made this view clearly untenable, as there is now obviously some causal connexion in the two families between tylosis and carcinoma of the oesophagus. As has already been stated, the occurrence of a new gene by mutation seems the most likely explanation, but if this is so the mutation rate must be exceptionally low, because (1) tylotic families have

TABLE III

Probability of Death from Carcinoma of the Oesophagus

(In the tylotic patients who do not die from some other cause)

Age 't'	*Probability of death before age 't'*
25	0·0019
30	0·0219
35	0·1024
40	0·2676
45	0·4806
50	0·6782
55	0·8226
60	0·9111
65	0·9587

never previously been reported to develop the neoplasm (and since we have become aware of the association six other tylotic families have been studied with a view to discovering it, each with negative results) and (2) in several large surveys of oesophageal cancer there has never been any evidence of familial concentration.

It is of considerable importance to try to calculate what proportion of the tylotic subjects can be expected to develop carcinoma of the oesophagus if they do not die earlier of some other cause. Table III gives this information in five-year periods. It will be seen that on the average, after the age of 35 years, between 15 and 25 per cent. of the tylotic subjects living at the beginning of any five-year period develop the carcinoma within that five-year period. By the age of 65, 95 per cent. of all the tylotics can be expected to develop carcinoma of the oesophagus, provided they do not die from some other cause. Even when we take this into account, it still seems that from 70 to 90 per cent. die of the carcinoma. This high proportion makes it very important that the persons at risk should be discouraged from excessive consumption of alcohol and tobacco and kept under close observation by their family doctor. That this may not be easy is shown by S IV, 4 who, although perfectly well on examination in 1956, developed an inoperable growth and died within 12 months. It may be that we are simply dealing with a single family containing a rare mutant gene, and that the interest in it is therefore restricted. It does, however, seem worth while to look out for similarly affected individuals elsewhere, in case the association has been overlooked or is due to environmental factors which have only recently started to operate. Furthermore, since the bronchus, like the oesophagus, is a derivative of the fore-gut, the possibility of an association between tylosis and squamous-cell carcinoma of the bronchus should also be borne in mind. We have, in fact, been told of one such case

(Everall, 1957). While this finding may be fortuitous, it may be useful in future to note the condition of the palms and soles of patients with bronchial carcinoma (as well as those with oesophageal cancer), in case an association of keratosis with the carcinomata is more common than has previously been thought. The problem is somewhat complicated by the fact that keratinization of the palms in response to manual work is very variable among normal people. Several heavy labourers whom we have seen with no family history of tylosis would, in a tylotic family, probably have been scored as affected. Whether such individuals are particularly prone to squamous-cell metaplasia if they develop lesions elsewhere is a matter of speculation. A consideration of other types of keratosis does not throw any light on the association we have noted. The problem of carcinoma of the stomach and acanthosis nigricans seems to be of a different nature, with no obvious genetic factors in the skin condition.

It is of interest to compare the carcinoma of the oesophagus in our families with the other cancers of man known to be determined by the action of a single gene. In some of these—familial polyposis coli, xeroderma pigmentosa, neurofibromatosis, and the Peutz syndrome—the cancer develops in a pre-existing lesion, whereas we have no evidence of there being any precancerous condition of the oesophagus in our tylotic patients. In another single-gene cancer of man, retinoblastoma, there is no precancerous lesion, but neither is there any associated benign lesion, as in the families we have reported.

We should like to express our thanks to the following for help with various aspects of the work: Lord Cohen of Birkenhead, Dr. E. B. Ford, F.R.S., Dr. R. L. Plackett, Dr. L. Findlay and members of the staff at Broadgreen Hospital, Liverpool, Dr. J. D. Macaulay, Dr. F. Whitwell, Dr. R. Winston Evans, Dr. E. Mavis McConnell, Dr. Seymour Smith, Dr. H. E. Vickers, Dr. J. H. Renwick, Dr. Sylvia D. Lawler, Dr. Douglas G. Freshwater, Dr. I. B. Sneddon, many General Practitioners, and Miss S. M. Manning. We are most grateful to the two surgeons, Mr. F. Ronald Edwards and Mr. J. R. B. Waddington, who had the care of many of the cancer patients, for making their records available to us. Finally, we wish to thank the Medical Research Committee of the United Liverpool Hospitals, the Medical Research Council, and the Nuffield Foundation for the grants towards our genetic research, without which this work could not have been undertaken.

Summary

A new association, that between keratosis palmaris et plantaris (tylosis) and carcinoma of the oesophagus, is described, occurring in two Liverpool families.

Eighteen cases of carcinoma of the oesophagus have occurred. There is unequivocal evidence that the neoplasm was associated with tylosis in 17 of the patients, and in only one has it been impossible to establish whether or not tylosis was present. No case of oesophageal carcinoma has occurred in members unaffected with tylosis.

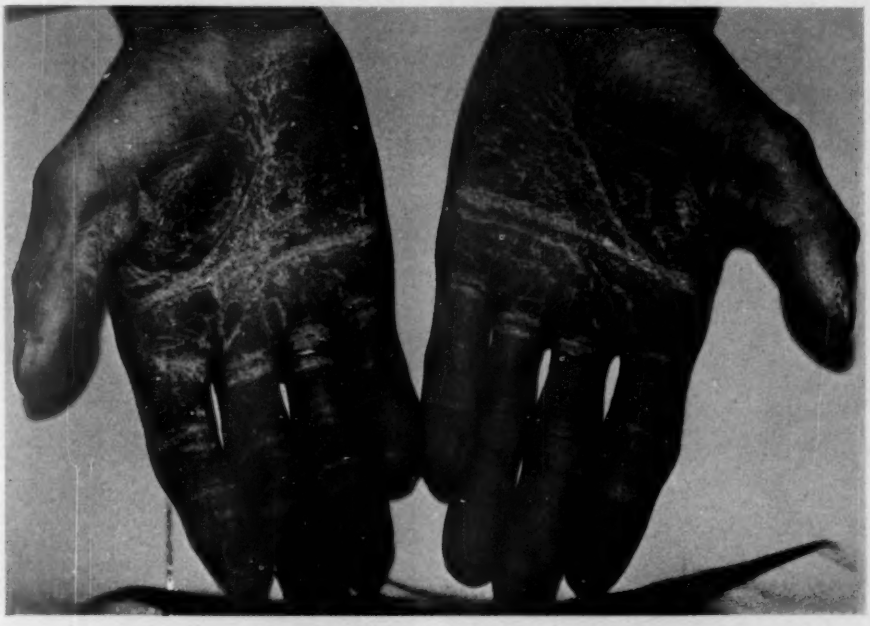

FIG. 3. Hands of S IV, 51, showing tylosis

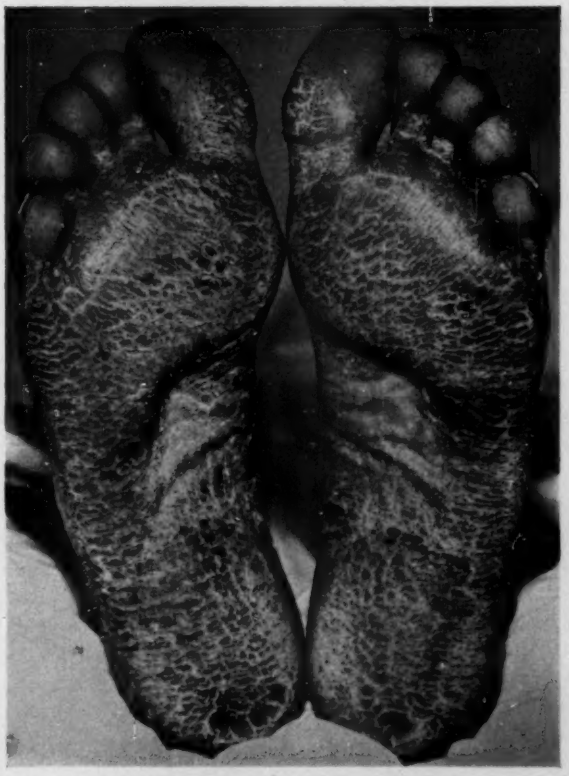

FIG. 4. Feet of S IV, 51, showing tylosis

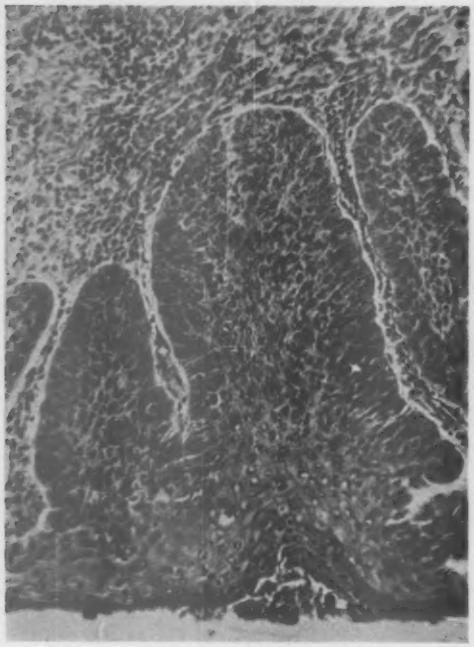

FIG. 5. Section from the edge of oesophageal carcinoma, showing its origin from the superficial stratified squamous epithelium (haematoxylin and eosin, ×130)

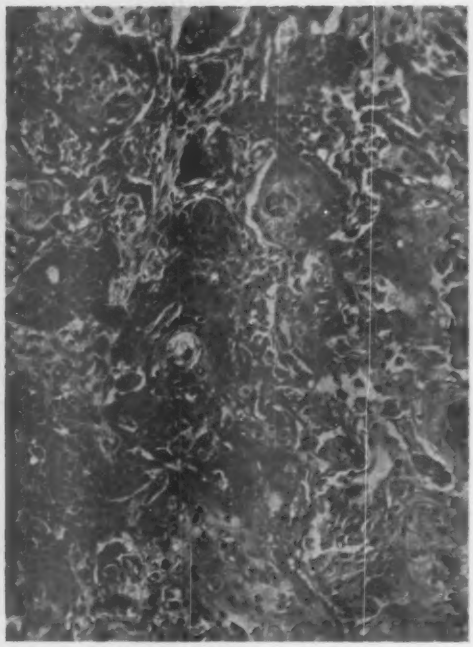

FIG. 6. Same tissue as the previous figure, showing the keratinizing infiltrating component of the growth (haematoxylin and eosin, ×110)

The data show that about 70 per cent. of those with tylosis eventually succumb to carcinoma of the oesophagus.

As is usually the case, tylosis in these families is inherited as an autosomal dominant. Although no connexion between the two families has been established, it is possible that they are, in fact, related. It is considered that the most likely explanation of the association is that it is due to a mutation of the normal tylotic gene; the possibility cannot be ruled out, however, that an environmental factor is operating on the normal gene for tylosis.

In the cases of carcinoma of the oesophagus in which the oesophageal epithelium adjacent to the tumour was examined histologically, no evidence of hyperkeratosis was found.

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616.37–07

THE DIAGNOSIS OF PANCREATIC DISEASE[1]

With Special Reference to a Test of Pancreatic Secretion utilizing both Secretin and Pancreozymin Stimulation

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With Plates 47 and 48

The pancreas is relatively inaccessible to clinical and radiological examination. Moreover, overt signs of pancreatic deficiency do not readily occur, because of the large functional reserve of the gland. The clinical diagnosis of pancreatic disease, therefore, is frequently dependent on laboratory procedures. Those in current usage include the examination of urine and faeces, of serum enzyme levels, and of duodenal fluid. The assessment of pancreatic function from an examination of duodenal fluid, representing mainly external pancreatic secretion, dates back to 1926, when Chiray, Salmon, and Mercier first employed secretin in man. The secretin test was further developed by a Swedish group of workers. Hammarsten, Ågren, Hammarsten, and Wilander (1933) produced a crystalline salt of the hormone, and Ågren and Lagerlöf (1936) and Ågren, Lagerlöf, and Berglund (1936) investigated pancreatic function in health and disease by measuring the volume, bicarbonate concentration, and activities of the enzymes amylase and trypsin, in the duodenal aspirate before and after secretin stimulation. The classic monograph of Lagerlöf (1942) added extensively to the knowledge of the subject, and further contributions were made by Diamond and Siegel (1940), Lake (1947), Dreiling and Hollander (1948, 1950), Dreiling (1950, 1951, 1953), Wirts and Snape (1951), and others. Although it is recognized that valuable diagnostic information may be obtained from the use of secretin stimulation, it has not been generally adopted as a routine test. Pancreozymin, first prepared by Harper and Raper (1943), has recently become available for use in the investigation of pancreatic function in man. This substance has a different effect on the pancreas from that of secretin: the latter produces a copious flow of juice of high bicarbonate and low enzyme content, whereas pancreozymin stimulates the production of enzymes only (Harper and Raper, 1943; Harper and Mackay, 1948). The Manchester group were the first to utilize pancreozymin, prepared by the method of Crick, Harper, and Raper

[1] Received November 14, 1957.

(1950), in combination with secretin as a test of pancreatic function (Duncan, Harper, Howat, Oleesky, and Varley, 1950; Howat, 1952). Pancreozymin prepared by this method contains, in addition, a material similar to or identical with cholecystokinin (Ivy and Oldberg, 1928), which causes contraction of the gall-bladder (Duncan, Harper, Howat, Oleesky, and Varley, 1950; Howat, 1952; Duncan, Evans, Harper, Howat, Oleesky, Scott, and Varley, 1953). Some Swedish clinics are now using a pancreozymin-cholecystokinin preparation together with secretin of high purity in the pancreatic function test (Jorpes and Mutt, 1956).

Usually the levels of amylase and lipase in the serum are not elevated except in the acute phases of pancreatic disease. So-called provocative blood enzyme tests have been introduced with a view to extending this type of examination to a wider range of pancreatic disorders. In these tests the enzyme activities of serum are measured at intervals before, and for several hours after, the administration of secretin, or of drugs known to stimulate the pancreas or constrict the sphincter of Oddi, or of both. The diagnostic value of serial determinations of amylase and lipase in the serum after combined secretin and pancreozymin administration has recently been reported (Burton, Hammond, Harper, Howat, Oleesky, and Varley, 1956). The pancreatic response to secretin stimulation persists for about 80 minutes or longer (Ågren and Lagerlöf, 1936; Dreiling and Hollander, 1950). Pancreozymin appears to have a shorter action, the effect being greatest during the first 10 to 15 minutes and often virtually complete by the end of 20 minutes after its injection. In the present study an 80-minute test was started after an alkaline fasting duodenal aspirate had been obtained. Secretin was injected at the commencement of the test, and was followed, after 60 minutes, by the administration of the rather crude preparation of pancreozymin used by the Manchester group.[2] A study was made of the composition of duodenal fluid after stimulation with secretin and pancreozymin, to determine the value of this method in the diagnosis of pancreatic disease. The activities of the enzymes amylase, trypsin, and lipase were measured to prove whether or not specific changes in the secretion of individual enzymes occurred in pancreatic disease. The test itself was under investigation, to determine how it might be applied in order to produce the maximum of diagnostic information with the minimum of effort. Serial determinations of serum-amylase were also carried out.

Methods

The patients studied were in the Gastro-Intestinal Unit and in the medical and surgical wards of the Western General Hospital. Their ages varied between 16 and 80 years.

Pancreatic function test. 1. A Levin tube with a small mercury-loaded bag was passed into the stomach on the night before the test. The patient was encouraged to sleep on his right side, to facilitate the passage of the tube into the duodenum. Sedation with a suitable barbiturate was given as a routine.

[2] Available from Boots Pure Drug Co. Ltd., Nottingham.

2. The fasting patient was examined radiologically on the morning of the test, and the end of the tube was adjusted to lie in the third part of the duodenum. If the tube had not entered the duodenum, it was withdrawn, and the test abandoned, to be repeated on another day.

3. A small nasal tube was passed into the stomach, and the patient was returned to the ward (Fig. 1).

4. Continuous suction was applied to both tubes, the duodenal aspirate being collected in a container immersed in ice.

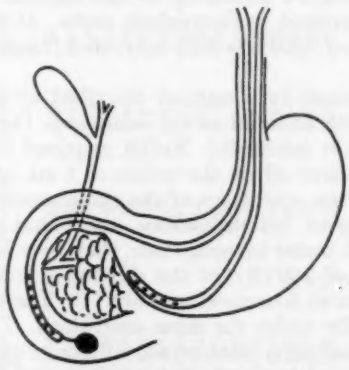

FIG. 1. Diagram showing the position of the Levin tubes for simultaneous collection of gastric and duodenal juice.

5. Collection of a basal 10-minute duodenal sample was commenced when the aspirate became alkaline.

6. Secretin (one unit per kg. body-weight) was given intravenously, and a 60-minute 'post-secretin' aspirate was collected. This consisted of two 10-minute followed by two 20-minute samples.

7. Pancreozymin (1·5 units per kg. body-weight, diluted in about 20 ml. of distilled water) was given by slow intravenous injection at the end of this 60-minute period, and a 20-minute 'post-pancreozymin' aspirate obtained. This usually comprised two 10-minute collections. Aliquot portions from each of the six samples were mixed with an equal volume of glycerine for enzyme estimations. These specimens were kept in ice-cooled test-tubes.

8. Patients being investigated for pain, possibly of pancreatic origin, were given a further injection of secretin (one unit per kg. body-weight) and morphine ($\frac{1}{6}$ gr. intravenously) at the end of the pancreozymin collection period.

The colour and pH of the duodenal and gastric aspirates were examined at frequent intervals throughout the test to ensure satisfactory collections of the respective secretions. The tubes were adjusted if necessary. The potency of the secretin used was 2·6 units per mg. The potency of the pancreozymin preparation varied between 3 and 4 units per mg.; the standard is assayed by the method of Crick, Harper, and Raper (1950).

The following determinations were made on the individual collections:

1. Volume.
2. Measurements of pH and of bicarbonate content by standard procedures.
3. The icteric index, as a measure of the content of bile-pigment.
4. Enzyme activity was investigated as follows:

Amylase was determined by a modification of the method of Lagerlöf (1942). After digestion with starch, the reducing material was determined by an alkaline copper method, instead of by the ferricyanide method formerly employed. Results were calculated according to Lagerlöf's formula, a factor being employed so that the final results were expressed in terms of Lagerlöf's units. The factor was derived from a comparison of the modified with the original method. Frequent checks were made for the presence of maltase, but this enzyme was always found to be absent.

Trypsin was determined according to the method of Gowenlock (1953). The results were expressed in Gowenlock units. It was assumed that the trypsin in the duodenal juice was fully activated (Lagerlöf, 1942; Gowenlock, 1953).

Lipase was determined by a method described by Sammons, Frazer, and Thompson (1956), with olive oil as the substrate. One unit represented the number of ml. of N/10 (alcoholic) NaOH required to neutralize the fatty acids liberated from olive oil by the action of 1 ml. of duodenal fluid, when treated according to the conditions of the stated method.

As the value of enzyme determinations was found to be affected by the stability of the enzymes under investigation, they were always completed without delay. The amylase activity of the duodenal fluid remained stable for periods up to three days at a temperature of 2° C. The lipolytic activity, however, deteriorated rapidly under the same conditions. The stability was found to be increased by the addition of an equal volume of glycerol to the duodenal aspirate, in accordance with the findings of Lagerlöf (1942). The output of bicarbonate, enzymes, and 'biliary pigments' (as measured by the icteric index) in the individual samples was calculated by multiplying the concentrations by the respective volumes. The output of these constituents during the 'post-secretin' hour and the 'post-pancreozymin' 20 minutes was calculated from the data so obtained, and the total output during the 80-minute period of the test was then determined. The 80-minute concentrations of bicarbonate, enzymes, and biliary pigment were calculated by dividing their total outputs by the respective volumes.

Provocative serum-amylase test. This test was carried out in 37 of the 48 patients subjected to duodenal intubation. Blood samples were taken at the commencement of the test, immediately before the injection of pancreozymin, and two hours after the conclusion of the test. The serum-amylase content of the samples was determined by the Wohlgemuth method (Harrison, 1947).

Other investigations. 1. Glucose tolerance. (1) A two-hour glucose-tolerance test was carried out after the oral administration of 1 g. of glucose per kg. body-weight. Venous blood-sugar was measured by the method described by Nelson and Somogyi (1953). (2) The provocative glucose-tolerance test, by means of cortisone loading (Duncan, 1956), was performed on one patient. 2. Fat-balance tests were carried out, fat being estimated by the method of van de Kamer, Huinink, and Weijers (1949).

Results

Fifty tests of pancreatic function by means of secretin and pancreozymin stimulation were performed on 48 patients. Nineteen had subsequently proven pancreatic disease, seven had disorders known to affect the pancreas, and in 19 there was no evidence of pancreatic disorder. A miscellaneous group comprised three patients. The 16 patients in whom subsequent investigations

TABLE I

Diseases not Normally Affecting the Pancreas

Case number	Sex and age (years)	Diagnosis	80-minute test: Total output: Volume (ml.)	HCO$_3^-$ (m-equiv.)	Amylase (units)	Trypsin (units)	Lipase (units)	80-minute concentration: HCO$_3^-$ (m-equiv.)	Amylase (units)	Trypsin (units)	Lipase (units)	Provocative serum-amylase test (initial/final) (Wohlgemuth units)
A. Unassociated with jaundice:												
33	M 49	Gastric ulcer	155	9·8	309	10,300	..	63	2·0	66	..	..
34	M 48	,,	229	10·9	690	31,180	5,360	48	3·0	136	23	5/5
35	M 55	,,	234	18·3	440	13,530	..	78	1·9	58	..	12/12
36	F 47	Duodenal ulcer	188	12·5	512	10,420	..	67	2·7	55	..	8/8
37	M 49	,,	257	18·8	1,389	29,010	8,380	74	5·4	113	33	5/8
38	F 20	Abdominal migraine	143	7·6	235	4,530	..	53	1·6	32	..	1/1
39	F 30	Abdominal epilepsy	125	6·6	316	15,350	..	53	2·5	123	..	**5/28**
40	M 38	Functional hypoglycaemia	147	9·3	552	3,430	..	63	3·8	23	..	..
41	F 40	Psychogenic	286	21·8	513	10,830	..	76	1·8	38	..	8/8
42	F 28	,,	192	13·7	703	15,190	..	71	3·7	79	..	5/5
43	M 38	Idiopathic steatorrhoea	299	13·9	792	9,290	..	48	2·7	32	..	5/5
44	M 39	Ileo-ileal fistula	202	17·3	388	19,790	5,180	85	1·9	98	26	5/5
45	F 62	Diverticulitis	254	19·3	585	5,640	..	76	2·3	22	..	12/12
46	M 45	Mesenteric calcification	181	11·4	734	24,630	7,540	63	4·1	136	42	5/8
47	F 50	Pyelonephritis	251	15·1	488	7,070	..	60	2·0	28	..	**5/13**
48	M 55	Coronary thrombosis	154	9·1	302	14,100	4,860	59	2·0	92	32	2/8
		Average	206	13·5	559	14,020	6,260	65	2·7	71	31	..
		Standard deviation	±54	±4·6	±280	±8,300	±1,590	±11	±1·0	±41	±7	..
B. Associated with jaundice:												
30	M 77	Carcinoma common bile-duct	159	10·8	**141**	7,330	..	**63**	**0·9**	**46**	..	..
31	F 75	Stricture common bile-duct	143	9·5	243	3,430	18,870	66	1·7	24	132	..
32	F 49	Carcinoma breast; metastases in porta hepatis	**70**	**5·0**	281	3,820	..	71	4·0	79	..	..

Values below the lower range of 'normal' are indicated by bold type.

failed to reveal evidence of either pancreatic or biliary disease were considered to have normal pancreatic function (Table IA). The total output and 80-minute

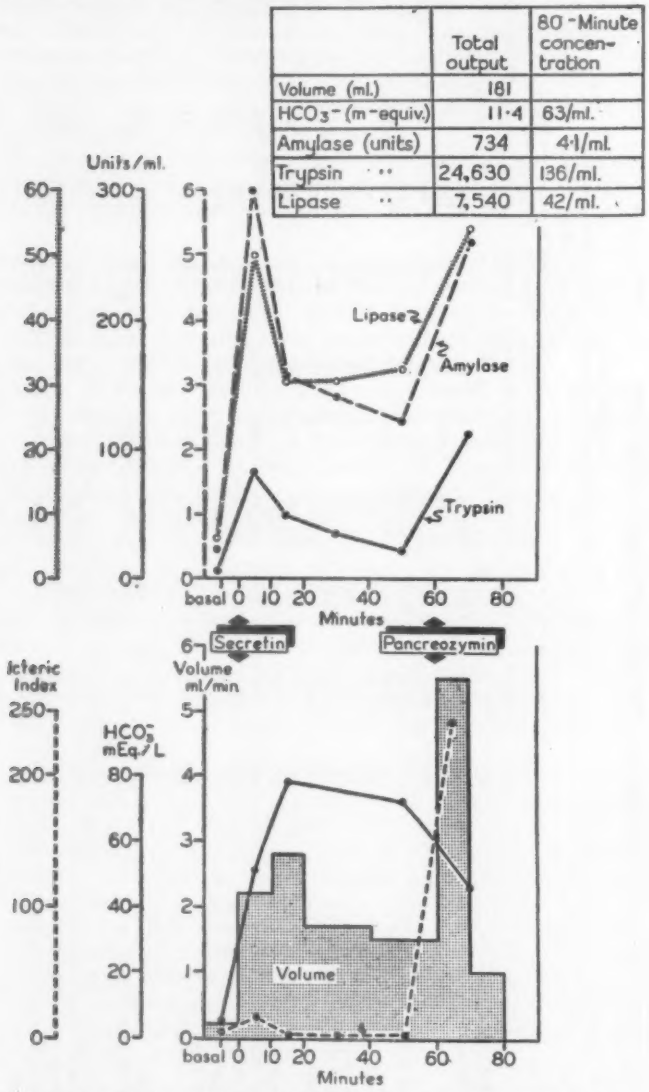

FIG. 2. Graphic illustration of a normal response to secretin and pancreozymin stimulation (80-minute collection of duodenal aspirate) (Case 46).

concentration of the constituents of the 80-minute duodenal aspirate obtained from each of these patients were used in calculating the average volume and the average output and concentration of bicarbonate and enzymes. The standard deviations of these constituents in the 16 'normal' tests are also included in

Table Ia. The post-pancreozymin component of the 80-minute collection in these 16 tests had an average volume of 57±19 ml., and average bicarbonate, amylase, and trypsin outputs of 3·2±1·1 m-equiv., 231±125 units, and 6,550±5,450 units respectively; it almost invariably contained a large amount of bile. The highest bicarbonate concentration attained in the post-secretin

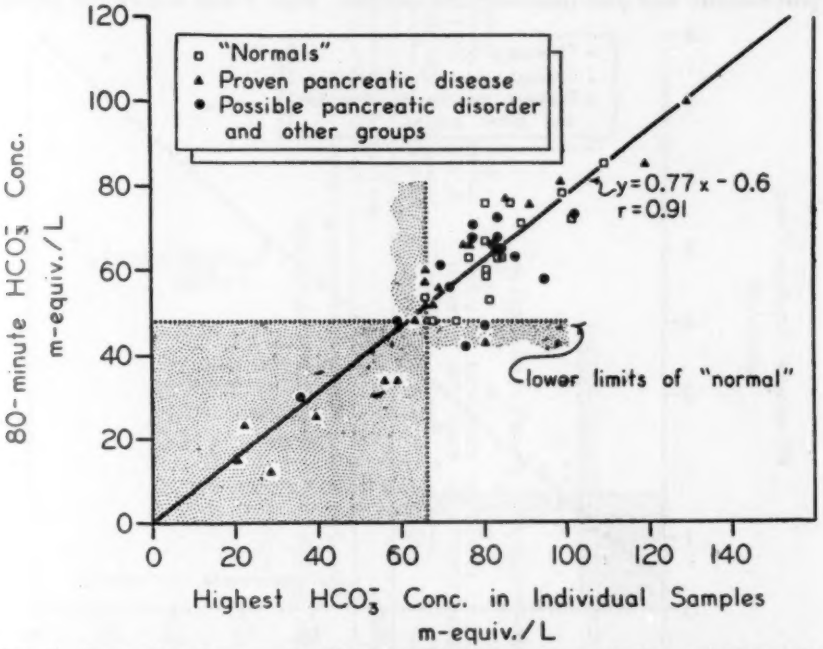

Fig. 3. Comparison between the 80-minute bicarbonate concentration and highest bicarbonate concentration in the individual samples of the corresponding test. Results enclosed in the shaded area are considered abnormal by both measurements.

fractions was greater than that in the corresponding post-pancreozymin fractions in 14 of the 16 tests, whereas the highest amylase and trypsin concentrations attained after pancreozymin were greater than those in the post-secretin samples in 11 and 14 of the 16 tests respectively. A rather typical response to secretin and pancreozymin is shown in Fig. 2 (Case 46).

An abnormal result was regarded as one in which one or more of the measured constituents of the 80-minute collection (volume; bicarbonate, amylase, lipase, or trypsin output or 80-minute concentration) was less than the lower limit of the range of 'normal'. Values slightly less than the lower limit of 'normal' (deviations less than 20 per cent.) were not, however, accepted as indicating abnormal pancreatic function, unless associated with a similar depression in at least one of the other measured constituents. Reduction of one of the measured constituents to less than 80 per cent. of the lower limit of 'normal', on the other hand, was accepted as evidence of abnormal pancreatic function.

The results were studied to determine whether estimations on the individual

10-minute and 20-minute collections were necessary, and whether separate post-secretin and post-pancreozymin samples need be examined. The total output and 80-minute concentrations were actually found to differentiate cases of proved pancreatic disease as well as the output and highest concentrations in the individual 10-minute and 20-minute fractions, derived from the separate post-secretin and post-pancreozymin samples. Figs. 3 and 4 show the highly

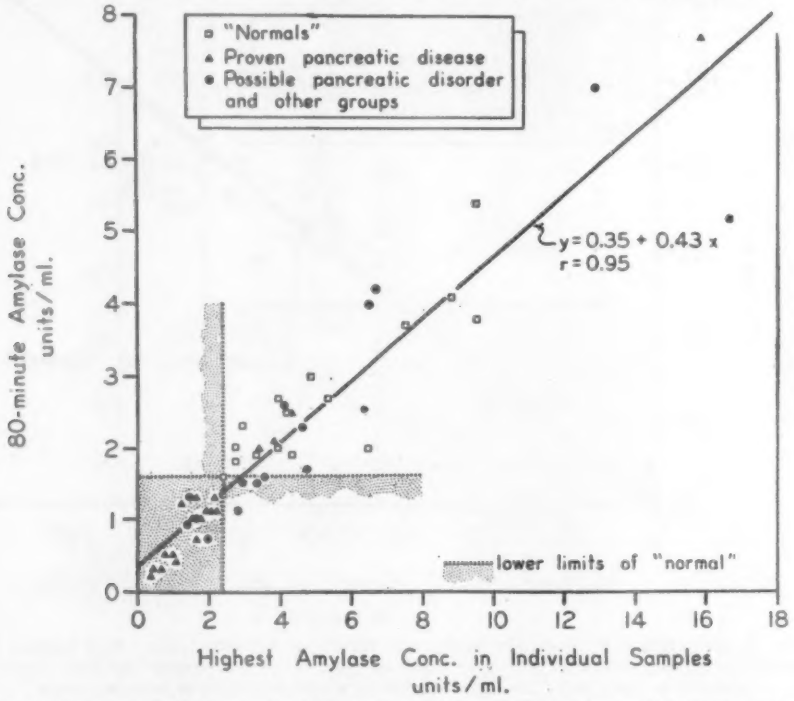

FIG. 4. Comparison between the 80-minute amylase concentration and highest amylase concentration in the individual samples of the corresponding test. Results in the shaded area are considered abnormal by both measurements.

significant linear correlations between the calculated 80-minute concentration and the highest concentration in the individual fractions comprising the corresponding total 80-minute period of the test for bicarbonate ($r = 0{\cdot}91$) and amylase ($r = 0{\cdot}95$) respectively, the coefficient of correlation having been calculated for each constituent from 50 pairs of values. Figs. 3 and 4 show also that information obtained from the pooled 80-minute collection was as adequate as that obtained from fractional samples in all but three of the 50 tests; three discrepancies in each set of data were found in patients with abnormal 80-minute concentrations, in whom the highest concentrations attained in the individual fractions of the corresponding tests were regarded as normal.

A comparison was made between the 16 'normal' and 26 abnormal results to determine which constituent of pancreatic secretion was most frequently disturbed in pancreatic disorder (Table II). The amylase response was almost

TABLE II

Comparison between the 16 'Normal' and 26 Abnormal Results

	Secretin and pancreozymin stimulation (80-minute collection)								
	Mean total output					*Mean 80-minute concentration*			
	Volume (ml.)	HCO_3^- *(m-equiv.)*	*Amylase (units)*	*Trypsin (units)*	*Lipase (units)*	HCO_3^- *(m-equiv./l.)*	*Amylase (units/ml.)*	*Trypsin (units/ml.)*	*Lipase (units/ml.)*
'Normal' results (16) . .	206±54	13·5±4·6	559±280	14,020±8,300	6,260±1,580	65±11	2·7±1·0	71±41	31±7
Abnormal results (26) . .	168±81	9·7±6·9	183±108	7,580±5,640	3,380±2,214	53±21	1·2±0·8	45±36	23±11
*P**	> 0·05	< 0·05	< 0·001	< 0·01	< 0·05	< 0·02	< 0·001	< 0·05	> 0·1

* Significance of the difference of the means measured by Student's *t* test.

TABLE III

Data obtained from Patients with Proved Pancreatic Disease

Diagnosis	*Case number*	*Sex and age (years)*	*Serum amylase*	*Jaundice*	*Steatorrhoea*	*Calcification*	*Glucose tolerance test*	*50-minute test: Total output: Volume (ml.)*	*50-minute test: Total output: HCO_3^- (m-equiv.)*	*50-minute test: Total output: Amylase (units)*	*50-minute test: Total output: Trypsin (units)*	*50-minute test: Total output: Lipase (units)*	*50-minute test: 80-minute concentration: HCO_3^- (m-equiv./l.)*	*50-minute test: 80-minute concentration: Amylase (units/ml.)*	*50-minute test: 80-minute concentration: Trypsin (units/ml.)*	*50-minute test: 80-minute concentration: Lipase (units/ml.)*	*Provocative serum-amylase test (initial/final) (Wohlgemuth units)*	*Findings at operation: Pancreatic*	*Findings at operation: Non-pancreatic*	*Operative treatment*
Chronic pancreatitis	1*	F 72	N	–	–	–	pD	267	20·1	60	9,920	..	75	0·2	37	..	2/5	Diffuse thickening	Cholelithiasis	Cholecystectomy and choledochostomy
	2*	M 58	N	–	++	–	pD	198	4·9	92	606	..	25	0·5	3	..	..	Head thickened	..	..
	3	M 58	N	Transient	++	–	N	104	1·6	35	618	..	15	0·3	6	..	..	Diffuse thickening	..	(Previous cholecystectomy)
	4†	M 47	N	–	++	++	D	60	0·7	17	376	..	12	0·3	6	..	5/5	..	..	..
Relapsing pancreatitis	5	M 72	N	Transient	–	–	N	176	10·1	1,350	28,800	7,460	57	7·7	164	42	8/13	Head thickened; F.N.	Chronic cholecystitis	Cholecystectomy and choledochostomy
	6*	F 56	+	–	–	–	N	208	16·0	233	7,190	..	77	1·1	34	..	5/8	No apparent disease	Cholelithiasis	Cholecystectomy and choledochostomy
	7*	F 38	N	–	–	++	N	179	11·8	231	15,040	..	66	1·3	84	..	5/8	Fibrotic pancreatic duct	..	Sphincterotomy
	8*	M 57	N	–	++	–	pD	201	6·7	195	8,160	..	34	1·0	41	..	5/8	Nodular; F.N.	..	Conversion of Polya to Billroth I
Pancreatitis secondary to peptic ulceration	9	M 60	N	–	–	..	..	367	31·2	444	9,460	..	85	1·2	26	..	8/13	Diffuse thickening	Penetrating D.U.	Polya gastrectomy
	10	F 52	+	–	–	..	..	243	16·2	476	5,280	..	66	2·0	22	..	*20/20*	Localized thickening	Penetrating G.U.	Polya gastrectomy
	11*	F 32	N	–	–	–	N	205	20·5	144	7,260	7,950	100	0·7	35	39	5/20	Head thickened	Penetrating D.U.	Gastroenterostomy and vagotomy
Haemochromatosis	12	M 42	N	–	..	–	D	197	10·3	214	15,020	3,570	52	1·1	76	20	5/8	..	..	..
	20	M 31	N	–	..	..	Prov.+	251	20·2	639	16,980	9,580	81	2·5	68	38	..	..	..	..
Pancreatic carcinoma:																		*Carcinoma*		
Ampullary	13	F 69	N	++	..	–	..	250	8·5	324	8,570	..	34	1·3	34	..	2/2	Ampulla, involving head of pancreas		Choledocho-enterostomy
	14*	F 59	+	Fluctuating	..	–	pD	60	1·4	126	2,500	1,190	23	2·1	42	20	*67/67*	Ampulla, with secondary pancreatosis		Whipple's operation
Head	15	F 80	..	++	..	–	..	74	3·2	37	1,150	..	43	0·5	16	..	5/5	Extensive in pancreas		Choledocho-enterostomy
	16	M 44	N	++	++	–	..	177	8·5	70	1,240	..	48	0·4	7	..	8/13	Extensive in pancreas		Choledocho-enterostomy
	17	F 77	..	++	..	..	..	195	11·6	203	3,010	..	60	1·0	15	..	5/5	Extensive in pancreas		Choledocho-enterostomy
Body	18*	M 62	+	–	++	–	D	68	3·8	72	422	..	56	1·1	6	..	*13/13*	Extensive in pancreas		Nil

Values below the lower range of 'normal', indicated by bold type, are regarded as abnormal. Persistently elevated serum-amylase values are in italics.
Jaundice ++ = serum bilirubin over 10 mg. per 100 ml. Steatorrhoea ++ = less than 82 per cent. absorption. Glucose tolerance test: N = normal; D = diabetic curve; pD = 'pre-diabetic' curve (normal fasting blood-sugar but abnormal glucose tolerance); Prov. + = abnormal glucose tolerance only after cortisone loading.
F.N. = fat necrosis. D.U. = duodenal ulcer. G.U. = gastric ulcer.
* Case reports given in Appendix.
† Case reported by Duncan, MacFarlane, and Robson (1958).

always impaired in patients in whom the test gave abnormal results. Reductions in the bicarbonate content and in the volume sometimes accompanied the diminished amylase secretion. Isolated reduction of trypsin or of lipase was seldom found. An impaired amylase response thus appeared the most sensitive index of disturbed pancreatic function.

TABLE IV

Analysis of Findings in Patients with Proved Pancreatic Disease

	Chronic pancreatitis		*Relapsing pancreatitis*		*Pancreatitis secondary to ulceration*		*Haemochromatosis*		*Carcinoma of pancreas*	
	Positive result	*Number tested*	*Positive result*	*Number tested*	*Positive result*	*Number tested*	*Positive result*	*Number tested*	*Positive result*	*Number tested*
Diagnosis confirmed by operation	3	3	3	4	3	3	..	..	6	6
Serum-amylase level elevated	0	4	1	4	1	3	0	2	2	4
Diabetes	1	4	0	4	0	3	1	2	1	6
Raised blood-sugar level or abnormal glucose-tolerance test	3	4	1	4	0	1	2	2	2	2
Frank steatorrhoea	3	4	1	4	0	3	..	..	2	2
X-ray changes:										
Calcification of pancreas	1	4	1	4	0	3	..	..	0	6
Duodenal displacement	0	4	0	4	0	3	..	..	2	6
Duodenal ulceration	0	4	0	4	2	3	..	..	0	6
Obstructive jaundice:										
Progressive	0	4	0	4	0	3	0	2	4	6
Fluctuating	0	4	0	4	0	3	0	2	1	6
Transient	1	4	1	4	0	3	0	2	0	6
Disease of gall bladder or common bile-duct	3	4	3	3	0	3	..	..	..	..
Pancreatic function test:										
Volume	2	4	0	4	0	3	0	2	3	6
Total output or 80-min. concentration, or both: HCO_3^-	3	4	1	4	0	3	0	2	4	6
Amylase	4	4	3	4	2	3	1	2	6	6
Trypsin	3	4	0	4	0	3	..	..	5	6
Lipase	..	..	0	1	0	1	1	1	1	1
Provocative serum-amylase test	0	2	1	4	2	3	0	1	1	6

Abnormal results were found in 16 of 19 patients with proved pancreatic disease (Tables III and IV), and the diagnosis was suggested by abnormal elevation of the serum-amylase in two of the three remaining patients. The other, a patient with haemochromatosis, showed normal pancreatic function. Abnormal results were found also in seven of the nine tests carried out on patients with possible (but unproved) pancreatic disorder (Table V). The miscellaneous (undiagnosed) group included a patient (Case 29) in whom pancreatic disease was suspected on the basis of undiagnosed upper abdominal pain and impaired pancreatic function. Recurrent attacks of deep venous thrombosis prompted the application of the pancreatic function test in Case 27; the output of trypsin was found to be markedly increased. The third patient in this group (Case 28), investigated because of persistent increase of serum-amylase, showed a very high amylase response after secretin and pancreozymin stimulation.

The cases of proven pancreatic disorder were considered from the point of

TABLE V

Data obtained from Patients with Possible Pancreatic Disease and in the Undiagnosed Group

Diagnosis	*Case number*	*Sex and age (years)*	*80-minute test*									*Provocative serum-amylase test (initial/final) (Wohlgemuth units)*
			Total output					*80-minute concentration*				
			Volume (ml.)	HCO_3^- *(m-equiv.)*	*Amylase (units)*	*Trypsin (units)*	*Lipase (units)*	HCO_3^- *(m-equiv./l.)*	*Amylase (units/l.)*	*Trypsin (units/l.)*	*Lipase (units/l.)*	
Possible pancreatic disease:												
Carcinoma of common bile-duct with spread	19	M 58	217	9·0	223	4,316	..	42	1·0	20	..	5/5
Sjögren's disease . .	21	F 40	111	6·2	258	12,010	3,120	56	2·3	108	28	..
Scleroderma . .	22	F 56	190	13·8	1,021	18,610	6,360	73	5·4	98	34	..
Polycystic disease; duodenal ulcer	23	F 40	121	8·2	188	2,980	..	68	1·6	25	..	5/5
Diabetes mellitus .	24 Apr. '55	M 23	165	7·7	419	3,720	..	48	2·6	23	..	..
	24 Nov. '55	24	204	6·1	307	12,700	..	30	1·5	62	..	5/5
Post-gastrectomy malabsorption; gastric ulcer	25 Apr. '55	M 50	281	17·2	371	7,750	..	61	1·3	28	..	*13/13*
	25 Nov. '55	51	213	10·9	158	27,170	1,850	47	0·7	118	8	..
Ulcerative colitis . .	26	F 15	117	7·4	172	9,000	2,300	63	1·5	77	20	5/5
Miscellaneous (undiagnosed) group:												
Reason for test:												
Recurrent thrombosis	27	M 32	266	15·3	1,127	43,320	..	58	4·2	163	..	5/5
Elevated serum amylase	28	F 54	190	13·8	1,314	16,660	..	73	7·0	87	..	*40/40*
Abdominal pain. (?) Pancreatitis	29	M 74	150	9·9	158	19,410	3,710	65	1·1	129	25	..

Values below the lower range of normal are in bold type. Persistently elevated serum-amylase values are in italics.

view of both the initial clinical picture and the clinico-pathological classification, to determine the full diagnostic value of the test.

A. *Clinico-pathological classification*

1. *Chronic pancreatitis* (Fig. 5). This group was characterized by disturbance of exocrine and, usually, of endocrine function, not associated with obvious pancreatic pain. One of the four patients (Case 1) was found to have a low amylase output and concentration as the only evidence of pancreatic disorder, the remaining three having grossly disturbed function of the pancreas.

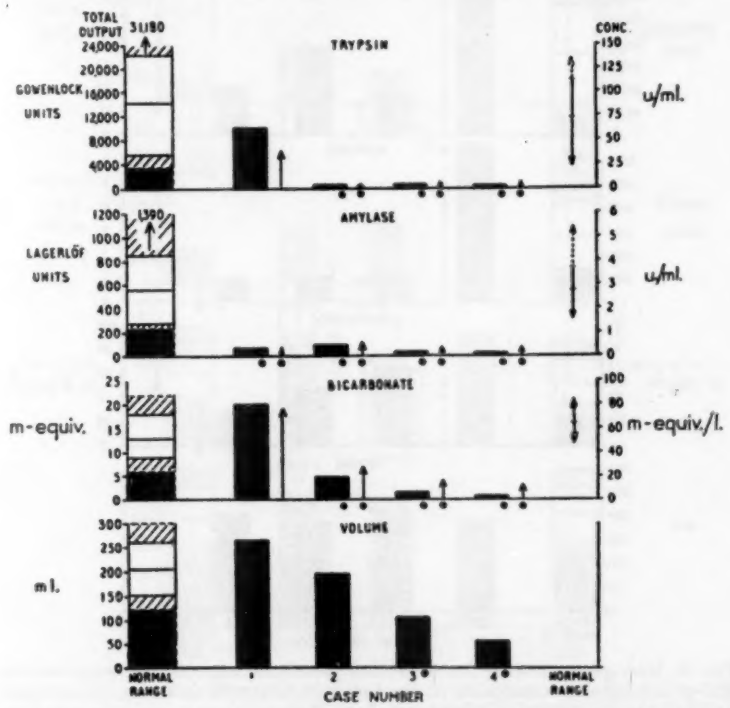

FIG. 5. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in the four patients with chronic pancreatitis. The volumes of pancreatic juice are indicated by blocks, and the total output and 80-minute concentration of bicarbonate, amylase, and trypsin by blocks and arrows respectively. The 'normal' values (average, standard deviation, and range) of total output and 80-minute concentration of these components are shown on the extreme left and right respectively. A black dot indicates an abnormally low value.

2. *Relapsing pancreatitis* (Fig. 6). Recurrent attacks of pancreatic pain constituted the main clinical feature in the patients of this group. The pancreatic function test gave a normal result in one patient (Case 5), but this was associated with a positive result in the provocative serum-amylase test. The three other patients all showed a poor amylase response, one of them (Case 8) showing in addition inadequate bicarbonate concentration.

3. *Pancreatitis secondary to peptic ulceration* (Fig. 7). Peptic ulceration, associated with bouts of prolonged and persistent upper-abdominal pain, radiating through into the back and eased slightly by leaning forward, suggested the possibility of penetration of the ulcer into the pancreas, with a resultant pancreatitis. This clinical syndrome was first described by Rivers (1947). Three patients, with subsequently proven pancreatitis secondary to peptic

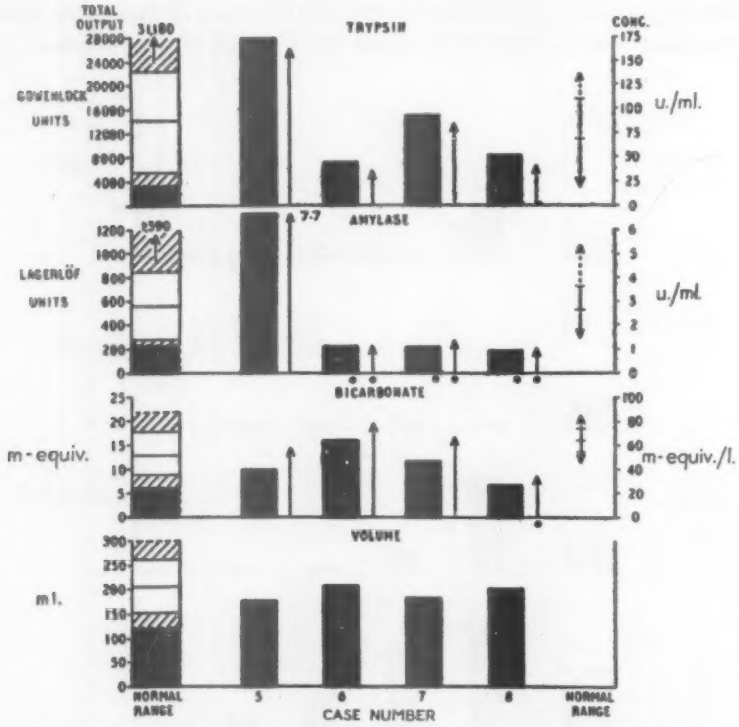

FIG. 6. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in the four patients with relapsing pancreatitis. For symbols see Fig. 5.

ulceration, were tested because of these suggestive symptoms. One patient (Case 11) showed grossly defective amylase secretion, and in another (Case 9) the amylase concentration was low, but the total output normal. The third patient tested (Case 10) had normal pancreatic function, but this was associated with a persistently elevated serum-amylase level.

4. *Haemochromatosis* (Fig. 8). An impaired amylase response was found in a patient with overt diabetes (Case 12). A second patient (Case 20) had normal pancreatic function, and showed normal glucose tolerance when tested by the standard method. The provocative glucose-tolerance test, however, suggested that his condition was pre-diabetic.

5. *Pancreatic carcinoma* (Fig. 9). (1) *Ampullary carcinoma.* Two patients

were tested. In one (Case 13) the amylase and bicarbonate concentrations were below normal, and at laparotomy the lesion was found to have involved the head of the pancreas. In the other (Case 14) the volume and total bicarbonate and enzyme output were reduced, although the enzyme concentrations were normal. The carcinoma was localized in the ampulla, but the remainder of the

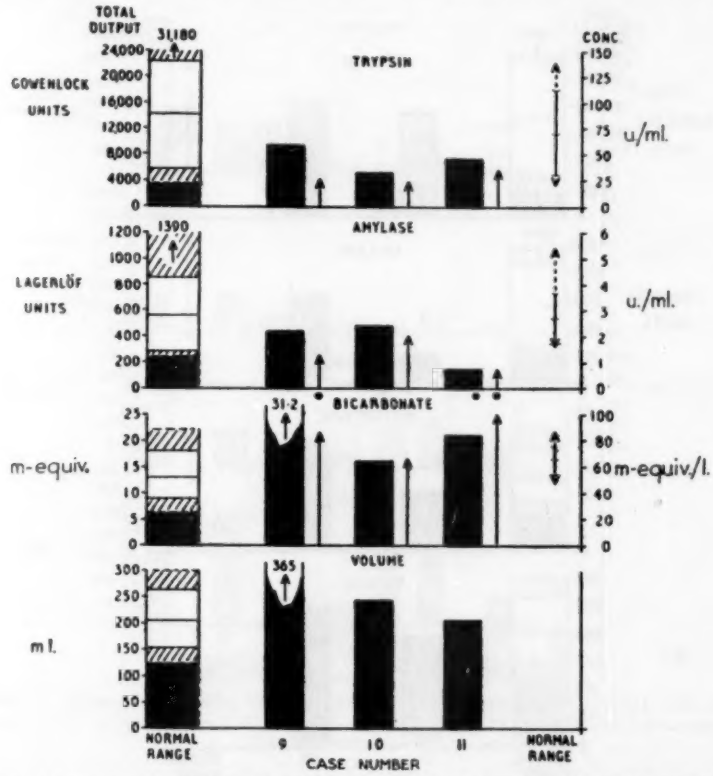

FIG. 7. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in the three patients with pancreatitis secondary to peptic ulceration. For symbols see Fig. 5.

pancreas was diffusely thickened by secondary pancreatosis, as shown histologically (Plate 48, Fig. 16). (2) *Carcinoma of the head of the pancreas.* Three patients with extensive involvement of the head of the gland were investigated, and found to have a defective secretion of enzymes. Gross pancreatic malfunction was present in one of these patients (Case 15). (3) *Carcinoma of the body of the pancreas.* Pancreatic function was grossly impaired in the one patient tested (Case 18).

B. *Initial clinical picture*

1. *Steatorrhoea* (Fig. 10). Tests of pancreatic function were carried out in seven patients with persistent steatorrhoea. The results were normal in two

patients, both of whom had evidence of small-intestinal disorder. One of them (Case 43) had classical idiopathic steatorrhoea, and in the other (Case 44) laparotomy showed an ileo-ileal fistula; the pancreas appeared normal. Impaired pancreatic function was present in the five remaining patients, all of whom had laparotomy or radiological evidence of pancreatic disease. Furthermore, four

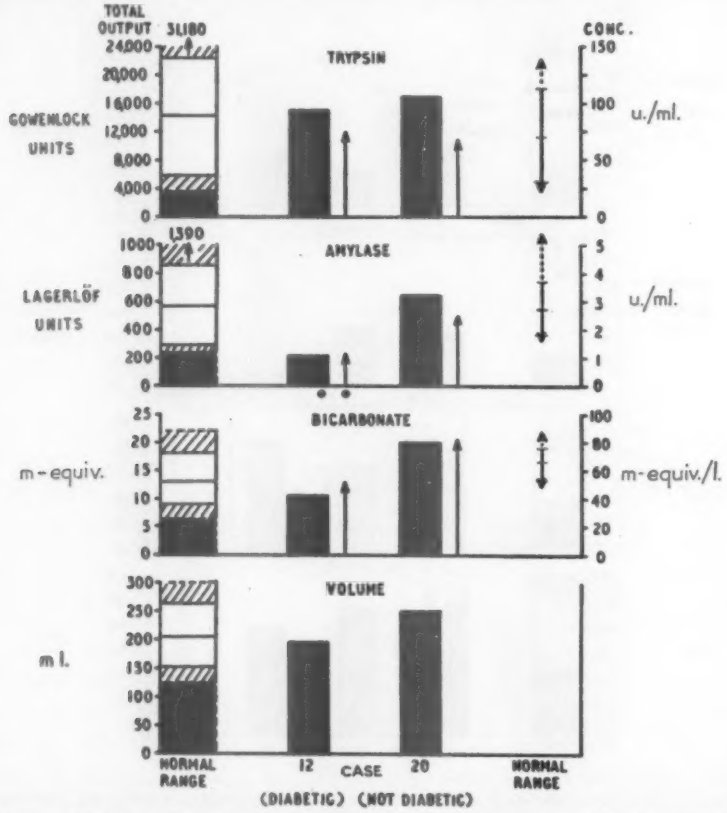

FIG. 8. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in the two patients with haemochromatosis. In Case 20 the provocative glucose-tolerance test was positive. For symbols see Fig. 5.

of these five patients showed diabetic (Cases 4 and 18) or pre-diabetic (Cases 2 and 8) glucose tolerance; the other (Case 3) had a normal glucose-tolerance curve. The steatorrhoea in one of these patients (Case 8) appeared to be due to a combination of pancreatic disease and a Polya gastrectomy rather than to pancreatic disease *per se*, and the finding of abnormally wide villi on jejunal biopsy in another (Case 2) raised the possibility of associated small-intestinal disorder; but the gross pancreatic malfunction, pre-diabetic glucose tolerance, and absence of macrocytosis in this patient suggested a pancreatic rather than a small-intestinal basis for the steatorrhoea. The three other patients with

pancreatic disease (Cases 2, 4, and 18) were also considered to have pancreatic steatorrhoea. It is of interest that ascorbic-acid saturation tests carried out in three of the patients with pancreatic disease (Cases 2, 3, and 8) all indicated impaired ascorbic-acid absorption, rather than abnormal utilization of the type described by Boscott and Cooke (1954) in patients with steatorrhoea and

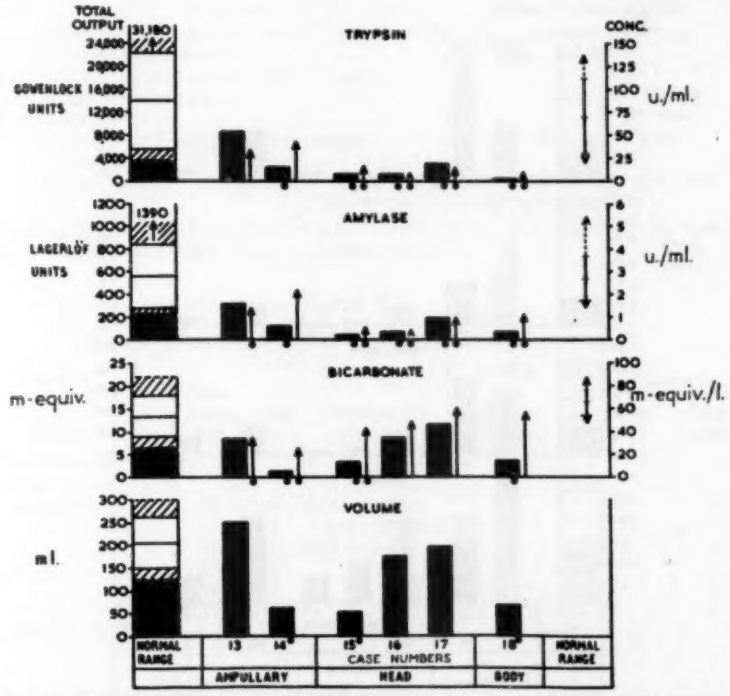

FIG. 9. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in the six patients with pancreatic carcinoma. For symbols see Fig. 5.

macrocytic anaemia, and found in our patient with idiopathic steatorrhoea (Case 43). Steatorrhoea was frequently present in patients with jaundice due to malignant obstruction of the common bile-duct. Pancreatic function was grossly disturbed in Case 16, and amylase secretion impaired in Case 30. The volume of the duodenal aspirate was abnormally low in Case 32. Four patients were investigated because of mild steatorrhoea. The possibility of pancreatic disorder could not be excluded in three of these patients with slightly impaired pancreatic function (Cases 24, 25, and 26).

2. *Abdominal pain* was a prominent symptom in 23 of the patients investigated. Ten patients in the group had pancreatic disease; eight of these had impaired pancreatic function (Cases 1, 3, 6 to 9, 11, and 18), and the other two showed normal external pancreatic secretion but an abnormal increase of serum-amylase (Cases 5 and 10). The pain in five of these 10 patients with

pancreatic disease was considered to be pancreatic in origin; suggestive radiation of the pain and postural relief were noted in four (Cases 9 to 11 and 18), and recurrent bouts of severe upper-abdominal pain, with more widespread radiation, in one (Case 7). In the remaining five patients pain was considered to be due to associated cholecystitis (Cases 1, 5, and 6) or small-intestinal colic

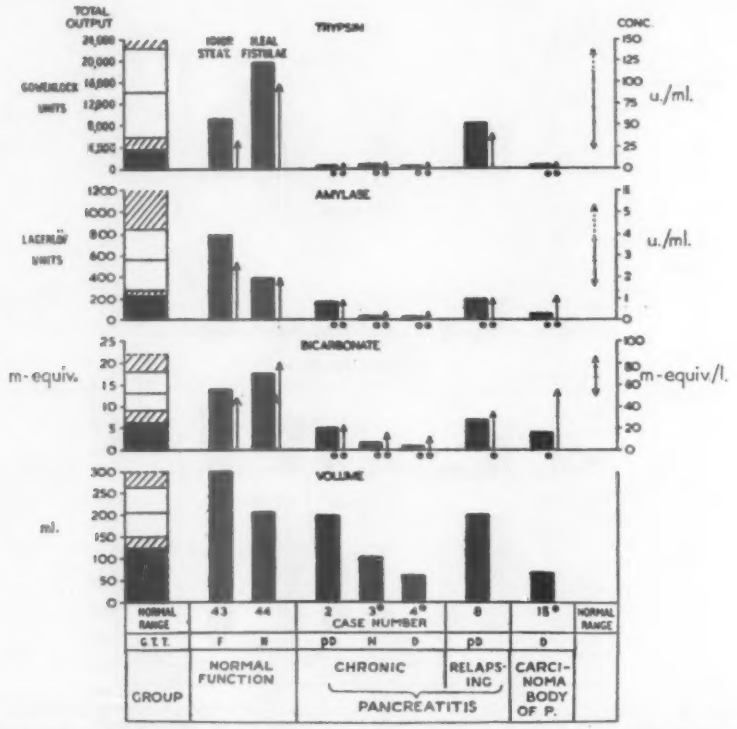

FIG. 10. Histogram showing the 80-minute pancreatic response following secretin and pancreozymin stimulation in seven patients under investigation for steatorrhoea. The results of the glucose tolerance test (G.T.T.) are indicated (N = normal response; F = 'flat' curve; pD = 'pre-diabetic' type of curve; D = diabetic response). For symbols see Fig. 5.

(Cases 3 and 8). A further 10 patients, who showed no evidence of pancreatic disease, yielded normal tests (Cases 33 to 38, 41, 42, 44, and 46). Abnormal results were found in the three remaining patients (Cases 29, 39, and 47). The provocative serum-amylase test was positive in two (Cases 39 and 47), but the abnormal result in each case could be ascribed to the administration of secretin and morphine during the test. Both patients showed normal external pancreatic secretion, and were considered to be free of pancreatic disease, in spite of the abnormal serum-amylase response. Pancreatic disease was suspected, but not confirmed, in one patient (Case 29) with impaired pancreatic function, included in the miscellaneous (undiagnosed) group.

Secretin and morphine were administered to all the patients who were investigated on account of abdominal pain. Morphine, which causes contraction

TABLE VI

Patients in whom Abdominal Pain was Reproduced by Pancreozymin

Case number	*Diagnosis*	*Effect of pancreozymin*
3	Chronic pancreatitis and ? small intestinal disorder	Colicky abdominal pain ++
8	Chronic pancreatitis and ? small intestinal disorder	„ „
44	Ileal fistula	„ „
46	? 'Mesenteric drag' from gross calcification	Dull lower abdominal pain
49	Crohn's disease of jejunum	Colicky abdominal pain and left lumbar hyperaesthesia

The post-pancreozymin secretion was not aspirated in Case 49, and the secretory response is therefore excluded from the present study.

TABLE VII

Results obtained in Patients with Obstructive Jaundice

Group	*Case number*	*Jaundice*	*Pancreatic secretion*	*Active gall-bladder disease*	*Provocative serum-amylase test*	*Red blood-cells in aspirate*
Pancreatic disease:						
Carcinoma ampulla (2)	13	+	Low amylase concentration	−	−	+
	14	±	Abnormal	−	++	+
head (3)	15	+	„	−	−	−
	16	+	„	−	+	+
	17	+	„	−	−	−
Pancreatitis (2)	3	±	„	−	−	−
	5	±	Normal	+	+	−
Possible pancreatic disease:						
Carcinoma of common bile-duct, with spread	19	+	Abnormal	−	−	−
Extrapancreatic obstruction:						
Carcinoma of common bile-duct	30	++	Low amylase concentration	−	..	−
Common bile-duct stricture	31	++	Normal	−	−	+++
Glands at porta hepatis	32	++	Low volume	−	−	+

Jaundice: ± incomplete; + clinically complete (bile present after pancreozymin); ++ complete (no bile after pancreozymin).
Provocative serum-amylase test: ++ persistent elevated value; + elevated after test.

of the sphincter of Oddi, diminishes the secretin-induced flow of pancreatic juice into the duodenum. Normally this effect is not associated with pain, and the flow may be restored by the inhalation of amyl nitrite. Secretin and morphine reproduced the pain in one of the patients investigated because of

abdominal pain (Case 7). This was a striking example of relapsing pancreatitis with gross ductal narrowing. The reproduction of severe pain by secretin and morphine was associated with virtual cessation of the flow of pancreatic juice into the duodenum. Amyl nitrite relieved the pain, and restored the flow of

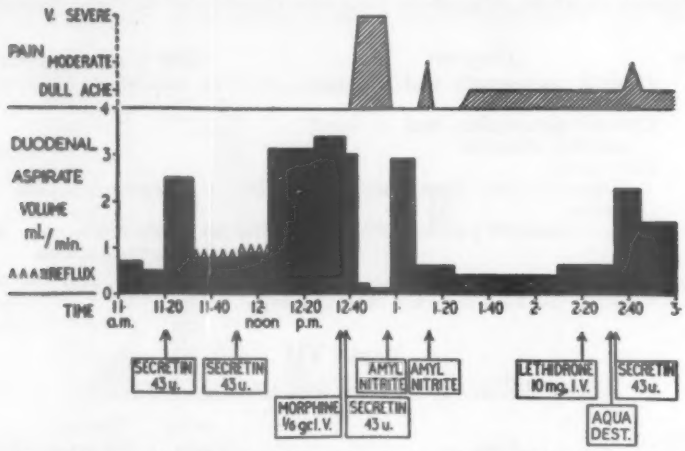

FIG. 11. Diagram showing the effect of secretin and morphine on the flow of pancreatic juice into the duodenum and on the reproduction of pain in Case 7.

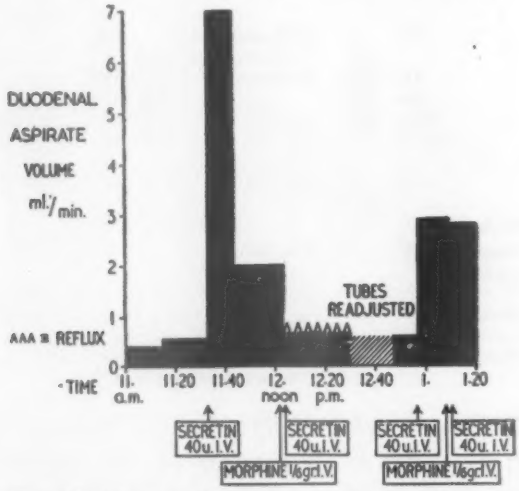

FIG. 12. Diagram showing the effect of secretin and morphine after sphincterotomy in Case 7. Pancreatic pain was not reproduced on this occasion.

pancreatic juice (Fig. 11). Secretin and morphine failed to reproduce the pain after sphincterotomy (Fig. 12). A pancreatic cause of abdominal pain was therefore suggested by the demonstration of impaired pancreatic function or by reproduction of the pain after the administration of secretin and morphine. Disturbed pancreatic function was, in fact, present in the patient whose pain

was reproduced by secretin and morphine. The pancreozymin preparation used in the present study was found to act not only on the pancreas, but also on the gall-bladder and the small intestine (Fig. 13). Increased bowel sounds, mild colic, and the passage of flatus frequently followed the injection of pancreozymin in normal subjects. It was thought that pancreozymin might reproduce pain due to disorder of the small intestine; this was found to be the case

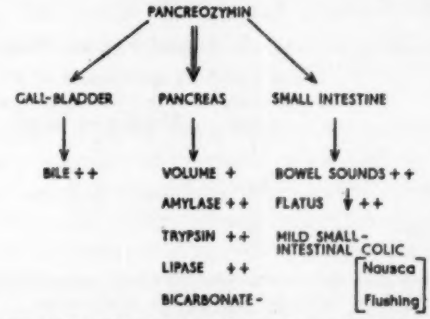

FIG. 13. Diagram to show the action of the pancreozymin preparation used in the present study. The profuse flow of bile into the duodenum following the administration of pancreozymin may be responsible for the increase in volume and diminished bicarbonate concentration of the duodenal aspirate.

in five of the patients investigated for abdominal pain (Table VI). Two of these patients (Cases 3 and 8) had pancreatic disease, but the pain was probably caused by adhesions following previous operations. In one of the patients (Case 3) the pain was not reproduced when atropine (gr. $\frac{1}{100}$) was given intravenously immediately before the administration of pancreozymin.

3. *Obstructive jaundice* (Table VII). Disordered pancreatic function was found in six of seven patients with pancreatic disease and obstructive jaundice. Active gall-bladder disease was, however, present in the remaining patient (Case 5), who had normal pancreatic function. Three patients with obstructive jaundice of extrapancreatic origin were investigated. A low amylase concentration was shown by one patient (Case 30), a slightly dehydrated 77-year-old man with carcinoma of the common bile-duct. In Case 32 the volume of the duodenal aspirate was low, but the bicarbonate and enzyme concentrations were normal. The third patient (Case 31) showed normal pancreatic function. The duodenal aspirate contained small amounts of blood in three of the five patients with obstructive jaundice due to pancreatic carcinoma (Cases 13, 14, and 16). A greater amount of blood, however, was present in the duodenal aspirate of the patient with stricture of the common bile-duct resulting from choledocholithiasis (Case 31).

Provocative serum-amylase tests (Table VIII)

The result of the provocative serum-amylase test was considered positive if the blood enzyme increased from an initial level of eight or less than eight

Wohlgemuth units to a subsequent level of 13 or more than 13 units two hours after injection of pancreozymin. It was positive in two of 14 patients considered to be free from pancreatic disease. Four of 16 patients with proven pancreatic disease gave positive results; these comprised three of 10 patients with pancreatitis, and one of six with carcinoma. The three positive results among the cases of pancreatitis occurred in patients who showed no evidence of advanced

TABLE VIII

Results of Provocative Serum-Amylase Tests

Group	*Number of patients tested*	*Positive (8 or < 8 to 13 or > 13 Wohlgemuth units)*	*Persistent elevation (13 or > 13 Wohlgemuth units)*
'Normal'	14	2	0
Pancreatic disease:			
Pancreatitis	10	3	1
Carcinoma	6	1	2
Possible pancreatic disease	5	0	1
Miscellaneous	2	0	1

Blood samples were taken at the commencement of the test, before the administration of pancreozymin, and two hours after the completion of the test.

pancreatic disease. One (Case 9) had a low amylase concentration in the duodenal aspirate, and another (Case 11) an impaired amylase output and concentration, whereas the third (Case 5) had normal pancreatic function. Neither steatorrhoea nor disturbed glucose tolerance was present in any of these three patients. The serum-amylase level was persistently elevated in a further three patients with pancreatic disease.

Discussion

The difficulties of duodenal intubation and the limited diagnostic value of the secretin test in patients with early disease of the pancreas have deterred many clinicians from using this test in the routine investigation of pancreatic disorder. An examination of the value of the pancreatic function test, in which both secretin and pancreozymin are employed as pancreatic stimulants, was prompted by the recent availability of a preparation of pancreozymin. The technique itself was under investigation, to determine the form which would produce most diagnostic information with a minimum of effort on the part of the patient, the doctor, and the biochemist. Lim, Matheson, and Schlapp (1923), in Sharpey-Schafer's laboratory in Edinburgh, first used two separate tubes for the simultaneous collection of gastric and duodenal juice. Our technique of passing a small tube overnight and a further small nasal tube in the morning was, in our experience, preferable to the passage of the rather thick double-lumen Lagerlöf tube. Patients were not unduly inconvenienced by the separate tubes, and the regularity in the passage overnight of a tube from the stomach into the duodenum (80 to 90 per cent. of intubations) avoided the delay frequently encountered in getting the Lagerlöf tube to enter the duodenum.

A satisfactory index of pancreatic function was obtained from the calculated total output and 80-minute concentration of bicarbonate and amylase in the

80-minute duodenal aspirate; the measurement of trypsin and lipase yielded no additional information. A reduced bicarbonate or amylase concentration provided valuable confirmatory evidence of pancreatic disorder in patients in whom the total output of these constituents was low. The association of a normal 80-minute concentration with a low volume suggested the presence of a localized obstruction of the pancreatic duct, or, possibly, unsatisfactory duodenal aspiration. The results show that an adequate index of pancreatic function may be obtained by determining the volume and the bicarbonate and amylase concentration of the pooled 80-minute collection after stimulation by secretin and pancreozymin.

Data from the 'normal' group of patients compared satisfactorily with those obtained in previously reported 80-minute secretin tests in similar patients. The volume of juice was closely comparable with that found in Dreiling and Hollander's series (1948), and slightly greater than that obtained by Diamond and Siegel (1940). The mean amylase output was somewhat lower than in the former series; but the lower range of amylase concentration was higher in our group. In the present study measurement of the amylase was found most useful in the diagnosis of pancreatic disease. Of the 19 patients with proved pancreatic disease who were tested, the volume was decreased in five, the bicarbonate response in eight, and the amylase response in 16. It is of interest that of the two patients with haemochromatosis, the one with overt diabetes (Case 12) showed evidence of exocrine malfunction (impaired amylase response), whereas the patient who had not yet developed diabetes had normal pancreatic function (Case 20). Decreased volume, considered by Dreiling and Hollander (1948) to be most characteristic of malignancy, was found in three of the six patients with pancreatic carcinoma.

The pancreatic function test was especially useful in the diagnosis of persistent steatorrhoea. Lagerlöf (1942) considered that an extrapancreatic cause was indicated in patients with steatorrhoea and normal pancreatic function; four of our five patients with pancreatic steatorrhoea showed evidence of extensive pancreatic disease. The remaining patient (Case 8) had a less marked impairment of pancreatic function, but the steatorrhoea in his case was thought to be due to the combination of mild pancreatic insufficiency with a Polya gastrectomy. The striking improvement after conversion of the Polya to a Billroth I gastrectomy suggested that a slight hold-up of pancreatic secretion in the afferent loop had been sufficient to convert an occult into an overt steatorrhoea (Plate 47, Fig. 14). The oral glucose-tolerance test proved of value in the diagnosis of pancreatic from non-pancreatic steatorrhoea, in agreement with the findings of Gaddie, Thomas, Smith, and French (1957). Impaired or frankly diabetic glucose tolerance was present in four of our five patients with pancreatic steatorrhoea; the patient with idiopathic steatorrhoea (Case 43), on the other hand, showed a flat glucose tolerance curve.

Pancreatic pain was absent or slight in the four patients classified as having chronic pancreatitis—the group in which gross disturbances of pancreatic function, both exocrine and endocrine, were most frequently manifest. One of the

patients (Case 1) had had a single attack of fulminating gangrenous pancreatitis 24 years previously, and was seen because of a five-year history of recurrent attacks of biliary colic; in two patients (Cases 2 and 4) the onset of pancreatic disease was insidious, and the course silent; the course in the fourth patient (Case 3) was punctuated by recurrent bouts of upper-abdominal pain, which were attributed mainly to biliary and small-intestinal disorders. Normal pancreatic function may be found in patients with pancreatic disease associated with pain (Lagerlöf, 1942; Dornberger, Comfort, Wollaeger, and Power, 1948). In the present series two of ten patients with proved pancreatic disease associated with pain showed a normal pancreatic response to secretin and pancreozymin; but a pancreatic cause of the pain in these two patients was suggested by disturbance of the serum-amylase level. The usefulness of the administration of secretin and morphine as a routine procedure in the investigation of possible pancreatic pain remains uncertain. This procedure, in addition to prolonging the test, frequently caused unpleasant side-effects. Pancreatic pain was reproduced in only one of the patients so tested (Case 7). The reproduction of the extremely severe pain was considered indicative of pancreatic disease, but the impaired pancreatic function in this patient would, in itself, have suggested the diagnosis. The reproduction of the pain, however, indicated the presence of gross abnormality of the pancreatic or the ampullary sphincter mechanism, or both; a sphincter abnormality was, in fact, found at operation. The recent development of pancreatography has facilitated the study of the pancreatic ductal system in patients submitted for operation on account of suspected pancreatic disease (Doubilet, 1957). This technique would appear to render unnecessary the routine use of secretin and morphine in the diagnosis of disorders of the pancreatic duct system.

A highly purified pancreozymin-cholecystokinin preparation, free of all 'intestine-contracting impurities', has recently been prepared by Jorpes and Mutt (1956) for the investigation of both pancreatic and gall-bladder function. Such impurities, unquestionably present in the rather crude pancreozymin preparation used in our study, were found useful in the elucidation of abdominal pain of small-intestinal origin. The effect of the preparation in causing contraction of the gall-bladder, due presumably to cholecystokinin, provided a reliable index of gall-bladder function, in agreement with the findings of Duncan, Evans, Harper, Howat, Oleesky, Scott, and Varley (1953) and Jorpes and Mutt (1956). The value of the pancreatic function test in the investigation of gall-bladder function will be the subject of a separate report.

Previous workers (Lagerlöf, 1942; Dreiling, 1951) have reported the value of the pancreatic function test in the diagnosis of obstructive jaundice. In their experience patients with uncomplicated disease of the gall-bladder or bile-ducts showed normal pancreatic function. In the present study normal pancreatic functio. .as present in only one of the three patients with obstructive jaundice of extrapancreatic origin who were investigated. The low level of amylase secretion in one of the patients (Case 30) may have been due to his poor general condition, and in another patient (Case 32) the possibility of unsatisfactory

duodenal aspiration could not be excluded. These facts make it unwise to attach undue significance to the results obtained in this small group.

Dreiling and Richman (1954) confirmed the doubts expressed by many previous workers regarding the diagnostic value of serum-enzyme changes after the administration of secretin or drugs known to stimulate the pancreas or constrict the sphincter of Oddi. Sun and Shay (1957), however, considered that the value of the secretin test was greatly enhanced if the serum-amylase and -lipase were estimated in conjunction with the results of duodenal aspiration, and were able to correlate the various combinations of results obtained with various combinations of damage to the secretory cells and ductal system of the pancreas. Burton, Hammond, Harper, Howat, Oleesky, and Varley (1956) reported that evidence of pancreatic disturbance could be obtained in a large proportion of patients with chronic pancreatic disease, by using the results of serial determinations of serum-amylase and -lipase after combined secretin and pancreozymin administration in conjunction with the glucose-tolerance test; the provocative serum-enzyme test was positive in the early stages of chronic pancreatitis and pancreatic carcinoma, whereas glucose-tolerance was increasingly impaired in the later stages. In the present study the patients with subsequently proved pancreatitis in whom the provocative serum-amylase test was positive showed normal glucose tolerance, and little or no evidence of pancreatic malfunction, when examined by the pancreatic function test. Significant elevations of the serum-amylase level, however, occurred in two of the patients considered to be free of pancreatic disease. These results, presumably 'false positives', may have been due to the administration of secretin and morphine, a combination of substances known to produce an increase of serum-enzymes in some normal subjects (Myhre, Nesbitt, and Hurly, 1949; Snape, Wirts, and Friedman, 1949). The provocative serum-enzyme tests were thus of limited diagnostic value. More helpful results might perhaps have been obtained if morphine and secretin had not been administered at the conclusion of the test, if the serum-lipase had also been measured, and if serial determinations had been carried out over a longer period of time.

The results of the present study appear to justify the use of a test of pancreatic secretory function utilizing both secretin and pancreozymin, together with the glucose-tolerance test and, possibly, the provocative serum-enzyme test. This diagnostic triad provides an important supplement to the clinical investigation of patients in whom pancreatic disease is suspected.

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APPENDIX

Illustrative Case Reports

Case 1. A housewife aged 71 years was admitted with a five-year history of recurrent bouts of persistent, but not very severe, upper-abdominal pain. These attacks were of up to three hours' duration, and were not associated with fever or jaundice. Twenty-four years previously she had had an attack of fulminating gangrenous pancreatitis, which settled satisfactorily after peritoneal drainage and cholecystostomy. There was radiological evidence of biliary calculi, and the common bile-duct appeared slightly dilated on intravenous cholangiography. The fasting blood-sugar was 67 mg. per 100 ml., but glucose tolerance was impaired. Fat-absorption was within normal limits. The pancreatic function test showed evidence of pancreatic insufficiency, and the variations in the icteric index of the samples of duodenal juice collected during the test suggested loss of gall-bladder function. At operation the cystic duct was found to contain numerous calculi, and there was slight narrowing at the lower end of the common bile-duct. The pancreas was diffusely thickened. Cholecystectomy and choledochostomy were carried out. The course after operation was uneventful.

Case 2. A railwayman aged 58 years was admitted with an 18-month history of diarrhoea, loss of weight in spite of satisfactory feeding, and slight shortness of breath on exertion. The patient presented a rather wizened appearance, and his loss of weight was obvious. The skin was thin and atrophic, with occasional small ecchymoses, and there were numerous angiomata of the face and neck. Gross clubbing of the finger-nails was noted. Examination of the chest showed evidence of chronic bronchitis and emphysema, and the ankles were slightly oedematous. The haemoglobin was 104 per cent., the white blood-cells 4,200 per cu. mm., and the erythrocyte sedimentation rate (Westergren) 7 mm. in the first hour. The serum-proteins were 5·1 g. (albumin 3·5 g.) per 100 ml., and the serum chloride, sodium, and potasium levels within normal limits. Sigmoidoscopy and barium enema gave negative results, but barium-meal examination showed numerous polypi in the pyloric antrum and well-marked coarsening of the mucosal pattern of the lower jejunum. No free acid was demonstrated in the gastric juice after maximal histamine stimulation. Stool microscopy revealed excessive amounts of muscle-fibres, fat-globules, and starch granules. Fat-balance studies showed only 81 per cent. absorption. The glucose-tolerance test was abnormal, the fasting blood-sugar being 94 mg. per 100 ml. and subsequent half-hourly readings 133, 228, 257, and 143 mg. per 100 ml. The pancreatic function test produced evidence of marked pancreatic disorder, the volume, bicarbonate content, and enzyme activity all being grossly deficient. Intravenous cholecystography indicated impaired gall-bladder function. Laparotomy, performed by Professor John Bruce in May 1954, revealed a brownish discoloration of the serous coat of the stomach and small intestine, with slight thickening of the latter. The superior aspect of the head of the pancreas was indurated, and 'almond icing' was observed on the lower pole of the spleen. The left lobe of the liver felt rather firmer than normal, and biopsy showed periportal fatty infiltration of the liver-cells, with a normal architectural pattern. A small antral polyp was removed, and found to consist histo-

logically of a submucous neurofibroma. Jejunal biopsy showed unusually wide villi, the increased width of the connective-tissue core being due to the presence of dilated lymphatics and a moderate increase in lymphocytes and plasma cells. No iron, melanin, or other brown pigment was seen in the serous coat of the jejunum or of the stomach. The course after operation was complicated by a transient but severe exacerbation of diarrhoea and malabsorption, and by bilateral bronchopneumonia, with a subsequent right-sided empyema which required surgical drainage. The patient's condition improved gradually during the next five months, by which time his weight was 7 lb. more than on admission. The liver, however, had enlarged to 4 cm. below the costal margin, and the result of a cephalin-cholesterol flocculation test, which was negative on admission, was now abnormal (+++). Fat-balance studies showed only 67 and 60 per cent. absorption in two three-day studies. Ascorbic-acid absorption was defective. After 16 days' oral administration (10 mg. of ascorbic acid per kg. body weight) there was no significant urinary excretion of ascorbic acid, but large amounts were excreted immediately after an intramuscular dose of ascorbic acid, given on the 17th day. The general condition of the patient has continued to improve, and his weight to increase, during the past 18 months. He has been taking pancreatin B.P. (up to 20 g. per day in divided doses) since his operation.

Case 6. A housewife aged 56 years was admitted with a seven-month history of recurrent attacks of severe colicky epigastric pain, radiating to the chest and through to the back. These attacks were of one to five hours' duration, and were not associated with fever, jaundice, or the passage of dark urine. The serum-amylase was increased to over 500 Somogyi units during the first attack. Cholecystography showed an adequately filled gall-bladder, containing numerous translucent calculi. The glucose-tolerance test gave normal results, and fat-balance studies showed normal absorption. The pancreatic function test produced evidence of mild pancreatic disorder. The variations in the icteric index of the samples of duodenal juice collected during the test suggested satisfactory gall-bladder function. At operation (October 1955) numerous small cholesterol stones were present in the gall-bladder, but the pancreas appeared normal. Cholecystectomy and choledochostomy were carried out. The course after operation was uneventful, and the patient has since had no further attacks of abdominal pain.

Case 7. A housewife aged 37 years was admitted in April 1954 with a nine-month history of recurrent attacks of excruciatingly severe upper abdominal pain, radiating through to the back, up to the shoulders, and down the arms. These bouts of pain lasted from five to 10 minutes, and tended to recur often during a period of a few hours. The pain was associated with nausea but no vomiting, was unrelated to meals, and was eased somewhat by the inhalation of amyl nitrite. The attacks became increasingly frequent, and were latterly of almost daily occurrence. Two years before her present admission the patient was investigated for pain in the lower chest, and was found to have cholelithiasis. Calcification was observed in the spleen and pancreas. Cholecystectomy and choledochostomy were performed by Professor John Bruce in January, 1953. In May 1954 the stool benzidine test, barium meal, analysis of urine, and intravenous pyelography all gave negative results. The serum-bilirubin was normal, and the common bile-duct appeared normal on intravenous cholecystography. Fat-absorption was satisfactory, and glucose tolerance was within normal limits. The secretin test of pancreatic function revealed an impaired

amylase output. The administration of morphine (gr. $\frac{1}{6}$ intravenously) with secretin, however, reproduced the severe pain, with a virtually complete cessation of the flow of pancreatic juice into the duodenum. Amyl nitrite relieved the pain and restored the flow of pancreatic juice (Fig. 11). Laparotomy, performed by Professor John Bruce in May 1954, confirmed the presence of gross narrowing of the pancreatic duct. Sphincterotomy, dilatation of the pancreatic duct, and choledochostomy were carried out. Secretin and morphine failed to reproduce the pain when administered four weeks after operation (Fig. 12). The patient remained free from symptoms for nine months, after which the abdominal pain recurred. The severity of the attacks increased during the next few months, and she was readmitted in November 1955. The pancreatic function test showed evidence of mild pancreatic insufficiency, and the pain was reproduced by the administration of morphine and secretin. The pain was again associated with a diminution in the duodenal aspirate, and was relieved by inhalation of amyl nitrite. This suggested that narrowing of the pancreatic duct had recurred. Bilateral sympathectomy was carried out in December 1955, since which time the patient has remained free from the abdominal pain.

Case 8. A boilerman aged 57 years was admitted in September 1955 with a four-year history of increasingly severe diarrhoea (up to 10 pale, buoyant stools per day), with the loss of over 15 lb. in weight. In October 1949 a Polya gastrectomy was performed for gastric and duodenal ulceration. The duodenal ulcer was dissected off the pancreas by the division of dense, almost cartilaginous, adhesions. The patient developed colicky abdominal pain, with borborygmi and visible paristalsis, shortly before his present admission. Examination of the abdomen revealed epigastric tenderness. Peristalsis was not visible, and the bowel sounds were not abnormally loud. There was radiological evidence of slight distension of the bowel with gas. A barium meal showed a normal gastric remnant, with a satisfactory function of the stoma. No ulcer was observed. The stools were bulky, greasy, and offensive, and on microscopic examination were found to contain excessive amounts of fat-globules and muscle-fibres. Fat-balance studies showed grossly impaired fat-absorption (50 per cent.), the stools containing 40 g. of fat per day during the test period. The nitrogen and protein content of the stool averaged 8 g. and 12 g. per day respectively. After the daily administration of ascorbic acid for 11 days (10 mg. per kg. body-weight, given orally) the excretion of ascorbic acid in the urine was unsatisfactory. Glucose tolerance was abnormal, the fasting blood-sugar being 65 mg. per 100 ml. and the subsequent half-hourly readings 147, 203, 197, and 167 mg. per 100 ml. The haemoglobin was 100 per cent., and the serum-proteins 7·3 per 100 ml. The serum-calcium was 8·4 mg. per 100 ml., and the inorganic phosphorus 3·5 mg. per 100 ml. Bone biopsy revealed no abnormality. Laparotomy was performed by Mr. Charles Falconer in October 1955. The efferent loop was distended in its proximal two feet, but there was no evidence of either extrinsic or intrinsic obstruction. The afferent loop was normal in length and appearance. The small bowel was diffusely thin and yellow in colour. The pancreas was small, firm, and diffusely nodular. Small patches of fat-necrosis were observed on the superior and inferior aspects of the pancreas and in the mesocolon. The Polya gastrectomy was converted to a Billroth I gastrectomy, and pancreatic biopsy performed. The specimen showed atrophy of many acini, ducts surrounded by dense fibrous tissue, and numerous areas of fat-necrosis (Plate 47, Fig. 14). The diarrhoea subsided immediately after operation, and a further fat-balance test two weeks after operation indicated normal fat-absorption (stool fat-content 3·5 g. per day). The stool nitrogen content in a three-day

collection period was 13·4 g. The pancreatic function test confirmed the presence of mild pancreatic insufficiency. Glucose tolerance was within normal limits three weeks after operation. No free acid was present in the gastric juice after maximal histamine stimulation (Plate 47, Fig. 14). The patient gained 18 lb. in weight during the subsequent nine months, and his general condition has continued to improve. Absorption of fat remains normal. Pancreatin B.P. (up to 20 g. per day in divided doses) was given for the first six months after operation.

Case 11. A housewife aged 32 years was admitted with an eight-year history of recurrent attacks of severe pain in the right hypochondrium. The pain radiated through the back, and was eased somewhat by leaning forward. These attacks lasted up to two days, diminishing gradually during the next few days. They were unrelated to meals, and were not associated with jaundice or the passage of dark urine. The patient's general condition had remained satisfactory, and her weight constant, during the eight years prior to admission. The haemoglobin was 90 per cent., and the erythrocyte sedimentation rate (Westergren) was 17 mm. after the first hour. Results of the stool benzidine test were repeatedly positive. There was radiological evidence of ulceration in the second part of the duodenum (Pl. 47, Fig. 15). The acid output from the stomach was 22 m-equiv. in the first hour after maximal histamine stimulation. Cholangiography showed an adequately filled gall-bladder, with a small fixed filling defect suggestive of a polyp. The diameter of the common bile-duct was within normal limits. Glucose tolerance was normal, and fat-balance studies suggested normal absorption. The pancreatic function test indicated mild, but definite, pancreatic disorder. The duodenal aspirate was free from bile until after the administration of pancreozymin. The result of the provocative serum-amylase test was positive. Laparotomy confirmed the presence of a large penetrating ulcer of the second part of the duodenum, with resultant localized pancreatitis. Vagotomy and gastroenterostomy were carried out.

Case 14. A housewife aged 59 years was admitted with a six-week history of vague ill-health, anorexia, and slight loss of weight, associated during the week prior to admission with jaundice, dark urine, and pale stools. The jaundice appeared to be diminishing when the patient was admitted. The haemoglobin was 72 per cent., and the uncorrected erythrocyte sedimentation rate (Westergren) 27 mm. after the first hour. The result of a stool benzidine test was positive, and the urine contained both bile and urobilin. There was a fluctuating bilirubinaemia (up to 4·2 mg. per 100 ml.) and persistently high level of serum alkaline phosphatase (up to 53 King-Armstrong units). Coarsening and marked irritability of the mucosa of the second part of the duodenum were observed radiologically. The gall-bladder was seen to be enlarged, but failed to concentrate dye. The pancreatic function test showed an impaired pancreatic response. Laparotomy, carried out by Mr. Charles Falconer in April 1956, revealed a carcinoma of the ampulla of Vater (histologically a papillary adenocarcinoma of the bile-duct) and induration of the pancreas (histologically an obstructive 'pancreatosis') (Plate 48, Fig. 16). Whipple's operation (resection of the head of the pancreas, duodenum, and pyloric antrum) was performed.

Case 18. A West Indian business man aged 62 years was admitted with a one-year history of increasingly severe, persistent epigastric pain, aggravated by lying down and eased somewhat by leaning forward. This pain was associated with lassitude and marked loss of weight. Retching and eructation were

frequent during the latter part of his illness. Mild diabetes was diagnosed three months before his admission. During the month preceding his admission the patient passed frequent, pale, bulky, and offensive stools. There was no family history of diabetes. On examination a firm, slightly tender epigastric mass was palpable. The liver was enlarged to 4 cm. below the costal margin. Stool microscopy showed excessive amounts of fat, and a single stool was found to contain 30 g. of fat. The fasting blood-sugar was 170 mg. per 100 ml., and the pancreatic function test indicated gross pancreatic disorder. Laparotomy confirmed the presence of an inoperable carcinoma of the body of the pancreas, with metastases in the liver and in the glands around the coeliac axis.

Summary

An 80-minute test of pancreatic exocrine function, utilizing both secretin and pancreozymin stimulation, is described. It is shown that sufficient diagnostic information may be obtained by determination of the volume, bicarbonate content, and amylase activity of the pooled 80-minute specimen of pancreatic juice. This test proved to be of value in the investigation of pancreatic disorders, and in particular in the diagnosis of pancreatic steatorrhoea. The earliest and most frequent finding in patients with pancreatic disease was a decrease in amylase secretion.

The value of the provocative serum-enzyme test in the diagnosis of early pancreatic disease, and of the glucose-tolerance test in overt pancreatic insufficiency, is discussed.

It is suggested that the pancreatic function test, the glucose-tolerance test, and possibly the provocative serum-enzyme test, constitute an important diagnostic triad, which is useful in the elucidation of various types of pancreatic disorder.

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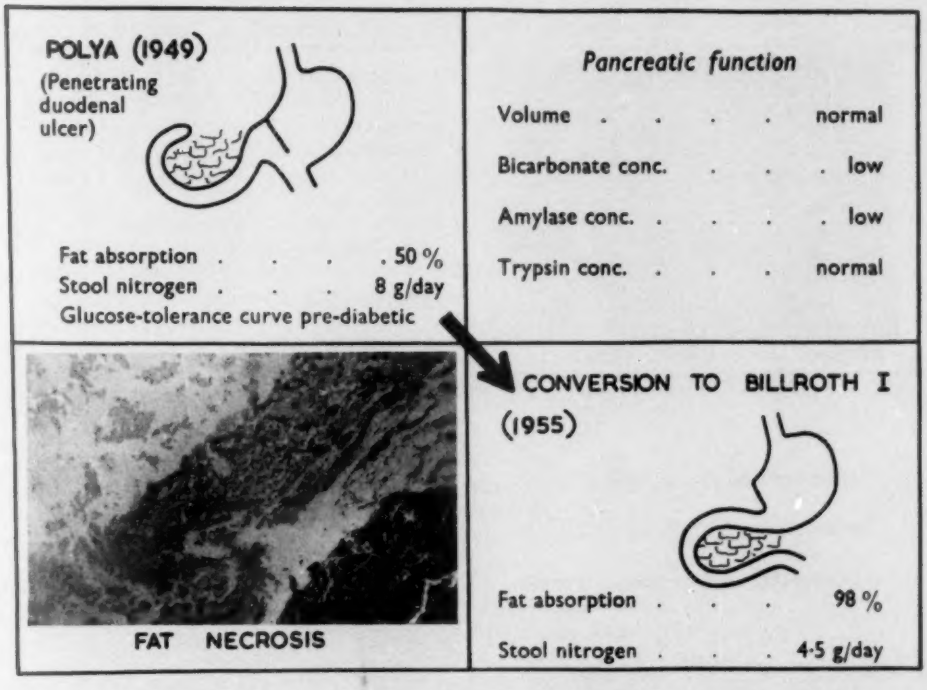

FIG. 14. Case 8. (Steatorrhoea after partial gastrectomy; chronic pancreatitis.) Composite diagram showing the effect of conversion of the Polya gastrectomy to a Billroth I gastrectomy. The photomicrograph shows an area of fat necrosis adjacent to the pancreas

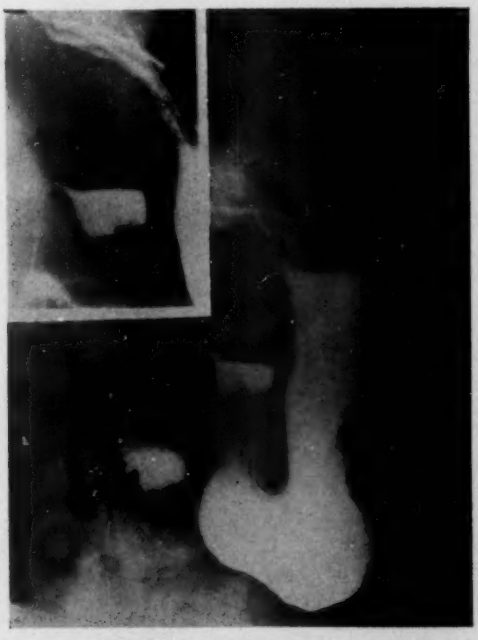

FIG. 15. Case 11. Barium meal showing the ulcer of the second part of the duodenum. Cholecystography was also carried out

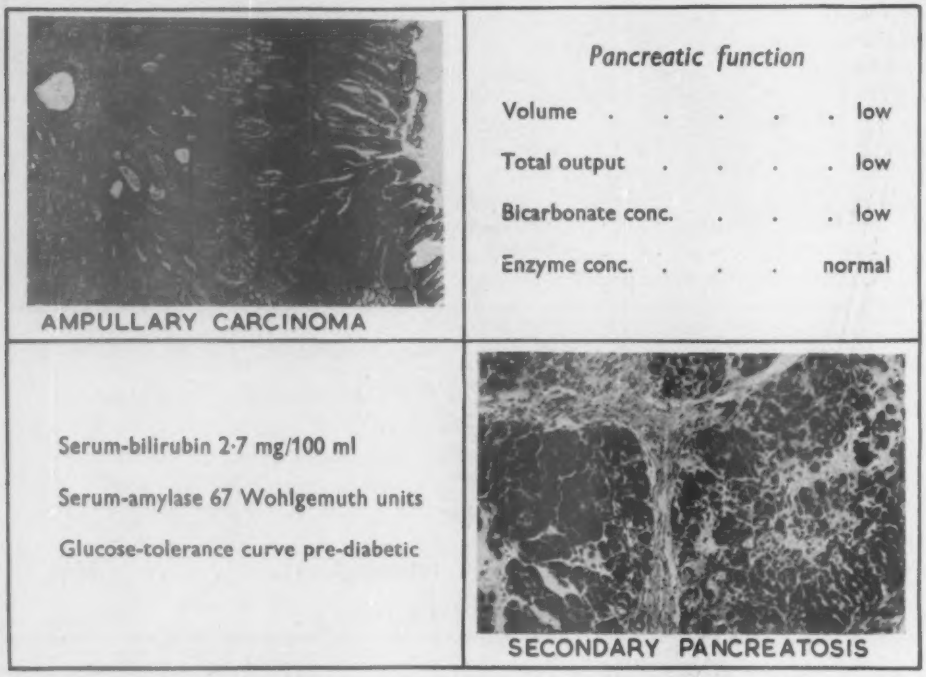

FIG. 16. Case 14. (Ampullary carcinoma with secondary pancreatosis.) Composite diagram showing the biochemical and histological findings

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